

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: **85304382.6**

(22) Date of filing: **19.06.85**

(51) Int. Cl.⁴: **C 07 D 307/79**
C 07 D 405/06, C 07 D 409/06
C 07 D 417/06, C 07 D 333/54
A 61 K 31/34, A 61 K 31/38
A 61 K 31/47, A 61 K 31/40
A 61 K 31/44, A 61 K 31/41

(30) Priority: **20.06.84 US 622372**

(43) Date of publication of application:
27.12.85 Bulletin 85/52

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: **MERCK FROSST CANADA INC.**
16711 Trans-Canada Highway
Kirkland Quebec(CA)

(72) Inventor: **Belanger, Patrice C.**
419 Promenade D'Avignon
Dollard des Ormeaux Quebec, H9B 1Y4(CA)

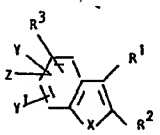
(72) Inventor: **Scheigetz, John**
279 Strasbourg
Dollard des Ormeaux Quebec, H9G 1R9(CA)

(72) Inventor: **Rokach, Joshua**
416 Place Canterbury Chomedey
Laval Quebec H7W 4G9(CA)

(79) Representative: **Crampton, Keith John Allen et al,**
D YOUNG & CO 10 Staple Inn
London WC1V 7RD(GB)

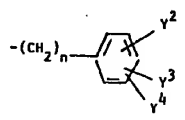
(54) Benzofuran and benzothiophene derivatives, their use in inhibiting mammalian leukotriene biosynthesis, and pharmaceutical compositions containing these derivatives.

(57) Novel benzofuran compounds have the formula



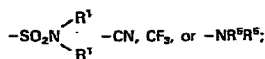
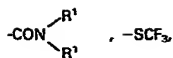
In which

each R¹ is independently hydrogen or C₁ to C₆ alkyl;
 R² is hydrogen, C₁ to C₆ alkyl, -(CH₂)_n -Het-Y, or



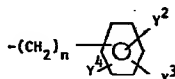
R³ is hydroxyl, O-
 C-R¹, O-
 C-OR⁴, OCOCH₂CH₂COOH,

OSO₃H, or OPO₃H₂;
 each R⁴ is independently C₁ to C₆ alkyl;
 each R⁵ is independently H, C₁ to C₆ alkyl, or both R⁵s
 join to form a 5- or 6-membered ring with the N to which
 they are attached;
 Het is a heterocyclic group selected from pyridine,
 pyrazine, pyrimidine, oxazole, pyrazole, oxadiazole, tetra-
 razole, quinoline, thiophene, furan, pyrrole, thiazole,
 thiadiazole, or imidazole;
 X is O, S, SO, SO₂;
 Y, Y¹, Y², Y³, Y⁴ and Z are each independently H,
 halogen, OH,
 C₁ to C₆ alkyl, C₂ to C₆ alkenyl,
 -COOR¹, -COR¹, nitro,
 C₁ to C₆ alkoxy, C₁ to C₆ alkylthio,
 -CH₂SR¹, OCH₂CO₂R¹,



and each n is independently 0 to 10;
with the provisos that:

- (a) not all of R^1 , R^2 , Y , Y^1 , Y^2 , Y^3 , Y^4 , and Z are simultaneously H;
- (b) when up to 2 of R^1 , R^2 , Y , Y^1 , and Z are C_1 to C_2 alkyl, and the others of R^1 , R^2 , Y , Y^1 , and Z are H, then R^2 is not OH; and
- (c) when n is



is 0 and one of R^3 , Y , Y^1
or Z is OH, then R^1 is not H or C_1 to C_2 alkyl.

Their pharmaceutically acceptable salts are also novel. These compounds are useful as inhibitors of mammalian leukotriene biosynthesis and are therefore useful therapeutic agents for treating allergic conditions, asthma, cardiovascular disorders, inflammation. The compounds are also useful as analgesics and as cytoprotective agents. They are made into pharmaceutical compositions for such uses.

- 1 -

17141Y

5 BENZOFURAN DERIVATIVES, THEIR USE IN INHIBITING
 MAMMALIAN LEUKOTRIENE BIOSYNTHESIS, AND
 PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

 This invention involves certain benzofuran
derivatives. These compounds are useful as
inhibitors of mammalian leukotriene biosynthesis. As
10 such, these compounds are useful therapeutic agents
for treating allergic conditions, asthma,
cardiovascular disorders and inflammation. The
compounds are also useful as analgesics and as
cytoprotective agents.

15 The leukotrienes are a novel group of
biologically active mediators derived from
arachidonic acid through the action of lipooxygenase
enzyme systems. There are two groups of leukotrienes

20

2882P/1043A

2884P/1045A

- 2 -

17141IA

derived from the common unstable precursor
Leukotriene A₄. The first of these are the
peptido-lipid leukotrienes, the most important being
Leukotrienes C₄ and D₄. These compounds
5 collectively account for the biologically active
material known as the slow reacting substance of
anaphylaxis.

The leukotrienes are potent smooth muscle
contracting agents, particularly on respiratory
10 smooth muscle but also on other tissues (e.g. gall
bladder). In addition, they promote mucous
production, modulate vascular permeability changes
and are potent inflammatory agents in human skin.
The most important compound in the second group of
15 leukotrienes is Leukotriene B₄, a dihydroxy fatty
acid. This compound is a potent chemotactic agent
for neutrophils and eosinophils and in addition, may
modulate a number of other functions of these cells.
It also affects other cell types such as lymphocytes
20 and, for example, may modulate the action of
T-suppressor cells and natural killer cells. When
injected in vivo, in addition to promoting the
accumulation of leukocytes, Leukotriene B₄ is also
a potent hyperalgesic agent and can modulate vascular
25 permeability changes through a neutrophil dependent
mechanism. Both groups of leukotrienes are formed
following oxygenation of arachidonic acid through the
action of a 5-lipoxygenase enzyme. See for example,
D. M. Bailey et al., Ann. Rpts. Med. Chem. 17 203
30 (1982).

The leukotrienes are potent spasmogens of
human trachea, bronchus and lung parenchymal strips,
and when administered to normal volunteers as

2882P/1043A

2884P/1045A

- 3 -

171411A

aerosols are 3,800 times more potent than histamine at inducing a 50% decrease in air flow at 30% of vital capacity. They mediate increases in vascular permeability in animals and promote mucous production in human bronchial explants. In addition, Leukotriene B₄ may also mediate mucous production and could be an important mediator of neutrophil and eosinophil accumulation in asthmatic lungs. 5-lipoxygenase products are also thought to be regulators of mast cell degranulation and recent studies with human lung mast cells have suggested that 5-lipoxygenase inhibitors, but not corticosteroids, may suppress antigen-induced mast cell degranulation. In vitro studies have shown that antigen challenge of human lung results in the release of leukotrienes and in addition purified human mast cells can produce substantial amount of leukotrienes. There is therefore good evidence that leukotrienes are important mediators of human asthma. 5-lipoxygenase inhibitors would therefore be a new class of drugs for the treatment of asthma. See, for example, B. Samuelsson, Science 220, 568-575 (1983).

Psoriasis is a human skin disease which affects between two and six percent of the population. There is no adequate therapy for psoriasis and related skin conditions. The evidence for leukotriene involvement in these diseases is as follows. One of the earliest events in the development of prepapillary lesions is the recruitment of leukocytes to the skin site. Injection of Leukotriene B₄ into human skin results in a pronounced neutrophil accumulation. There are gross abnormalities in

2882P/1043A

2884P/1045A

- 4 -

17141IA

arachidonic acid metabolism in human psoriatic skin. In particular, highly elevated levels of free arachidonic acid can be measured as well as large amounts of lipoxygenase products. Leukotriene B₄ has been detected in psoriatic lesions, but not in uninvolved skin, in biologically significant amounts.

Leukotrienes can be measured in nasal washings from patients with allergic rhinitis and are greatly elevated following antigen challenge. Leukotrienes may mediate this disease through their ability to regulate mast cell degranulation, by modulating mucous production and mucociliary clearance and by mediating the accumulation of inflammatory leukocytes.

Leukotrienes can also mediate other diseases. These include atopic dermatitis, gouty arthritis, and gall bladder spasms. In addition, they may have a role in cardiovascular disease because leukotrienes C₄ and D₄ act as coronary and cerebral arterial vasoconstrictors and these compounds may also have negative inotropic effects on the myocardium. In addition, the leukotrienes are important mediators of inflammatory diseases through their ability to modulate leukocyte and lymphocyte function.

SUMMARY OF THE INVENTION

It has now been discovered that certain substituted benzofurans and benzothiofurans of Formula I are effective inhibitors of leukotriene biosynthesis. Thus, these compounds are useful therapeutic agents for treating conditions such as asthma, allergies, cardiovascular disorders such as

2882P/1043A

2884P/1045A

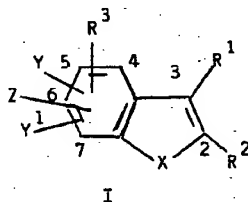
- 5 -

171411A

angina and inflammation, for amelioration of skin diseases like psoriasis and atopic eczema, and as cytoprotective agents.

5 DETAILED DESCRIPTION OF THE INVENTION

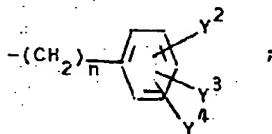
The compounds of the present invention are compounds of the formula:



wherein:

each R^1 is independently hydrogen or C_1 to C_6 alkyl;

R^2 is hydrogen, C_1 to C_6 alkyl,
 $-(CH_2)_n$ -Het-Y, or



R^3 is hydroxyl, $O-C(=O)-R^1$, $O-C(=O)-OR^4$, $OCOCH_2CH_2COOH$, OSO_3H ,
 or OPO_3H_2 ;

each R^4 is independently C_1 to C_6 alkyl;
 each R^5 is independently H, C_1 to C_6 alkyl, or both
 R^5 s join to form a 5- or 6-membered ring with the N
 to which they are attached;

2882P/1043A

2884P/1045A

- 6 -

171411A

Het is a heterocyclic group selected from
pyridine, pyrazine, pyrimidine, oxazole,
pyrazole, oxadiazole, tetrazole, quinoline,
thiophene, furan, pyrrole, thiazole, thiadiazole,
or imidazole;

X is O, S, SO, SO₂;

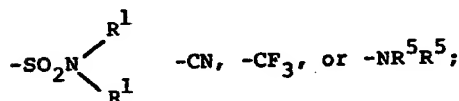
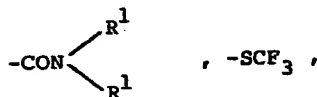
Y, Y¹, Y², Y³, Y⁴ and Z are each
independently H, halogen, OH,

C₁ to C₆ alkyl, C₂ to C₆ alkenyl,

-COOR¹, -COR¹, nitro,

C₁ to C₆ alkoxy, C₁ to C₆ alkylthio,

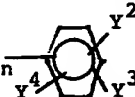
-CH₂SR¹, OCH₂CO₂R¹,



and each n is independently 0 to 10;

with the provisos that:

- (a) not all of R¹, R², Y, Y¹, Y², Y³, Y⁴, and Z
are simultaneously H;
- (b) when up to 2 of R¹, R², Y, Y¹, and Z are C₁ to
C₂ alkyl, and the others of R¹, R², Y, Y¹, and Z
are H, then R³ is not OH; and

- (c) when n in $-(\text{CH}_2)_n$  is 0 and one of R³,
Y, Y¹ or Z is OH, then R¹ is not H or C₁ to C₂
alkyl;

and the pharmaceutically acceptable salts thereof.

2882P/1043A

2884P/1045A

- 7 -

171411A

Unless otherwise indicated, the alkyl groups or alkyl portions of other groups may be straight chain, branched or cyclic or may contain both straight chain or branched and cyclic portions.

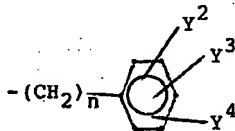
5 By halogen is meant fluorine, chlorine, bromine or iodine.

The heterocycles of $-NR^5R^5$ when R^5R^5 are joined include pyrrolidine, piperidine, and morpholine.

10 Preferred compounds of the present invention are compounds of Formula I as defined above, wherein:

each R^1 is C_1 to C_3 alkyl;
 R^2 is hydrogen, C_1 to C_3 alkyl,

15



20

or $-(CH_2)_n-$ Het-Y;

25 R^3 is hydroxyl, $O-\overset{\overset{O}{\parallel}}{C}-R^1$, $O-\overset{\overset{O}{\parallel}}{C}-OR^4$, $OCOCH^2CH^2COOH$, OSO^3H , or OPO^3H_2 ;

each R^4 is independently C_1 to C_3 alkyl;

Het is heterocyclic group selected from pyridine, quinoline, thiazole, thiadiazole, or imidazole;

X is O or S;

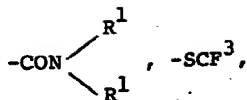
30 Y, Y^1 , Y^2 , Y^3 , Y^4 , and Z are each independently H, halogen C_1 to C_3 alkyl, C_2 or C_3 alkenyl, $-COOR^1$, $-COR^1$, C_1 to C_3 alkoxy, C_1 to C_3 alkylthio, $-CH_2SR^1$,

2882P/1043A

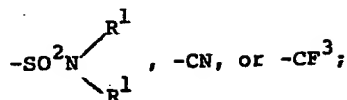
2884P/1045A

- 8 -

171411A



5



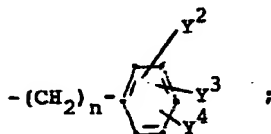
10

Y^2 is also $\text{OCH}_2\text{CO}_2\text{R}^1$;
each n is independently 0 to 4;
and the pharmaceutically acceptable salts thereof.

More preferred compounds of the present
invention are compounds of the Formula I as defined
above, wherein:

each R^1 is methyl;
 R^2 is hydrogen,

20



25

or $-\text{CH}_2-\text{Het}-\text{Y}$;
 R^3 is 4-hydroxyl, 4- OSO_3H , or 4- OPO_3H_2 ;
 Het is a pyridine;
 $n = 1$ or 2 ;
 X is O ; and
 Y , Y^1 , Y^2 , Y^3 , Y^4 , and Z are each independently
 H , fluorine, chlorine, methyl, propyl, allyl,
 $-\text{COOR}^1$, $-\text{COR}^1$, methoxy, methylthio,
 $-\text{CH}_2\text{SR}^1$, or $-\text{CF}_3$;

30

and the pharmaceutically acceptable salts thereof.

2882P/1043A

2884P/1045A

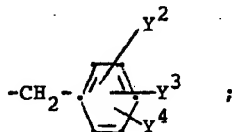
- 9 -

171411A

Most preferred compounds of the present invention are compounds of Formula I as defined above, wherein:

each R^1 is methyl;

5 R^2 is



10

R^3 is 4-hydroxyl, 4-OPO₃H₂, or 4-OSO₃H;

Het is a pyridine;

X is O; and

Y, Y¹, Y², Y³, Y⁴, and Z are each independently

15 H, fluorine, chlorine, propyl, allyl, methoxy, or CH₂SR¹;

and the pharmaceutically acceptable salts thereof.

Other most preferred compounds of the present invention are compounds of Formula I as

20 defined above, wherein:

each R^1 is methyl;

R^2 is hydrogen;

R^3 is 4-hydroxyl, 4-OPO₃H₂, or 4-OSO₃H;

Het is a pyridine;

25 X is O; and

Y, Y¹, Y², Y³, Y⁴, and Z are each independently

H, fluorine, chlorine, propyl, allyl, methoxy, or CH₂SR¹;

and the pharmaceutically acceptable salts thereof.

30 Still other most preferred compounds of the present invention are compounds of Formula I as defined above, wherein:

each R^1 is methyl;

R^2 is -CH₂Het-Y;

2882P/1043A

2884P/1045A

- 10 -

17141IA

R^3 is 4-hydroxyl, 4- OPO_3H_2 , or 4- OSO_3H ;

Het is a pyridine;

X is O; and

Y, Y^1 , Y^2 , Y^3 , Y^4 , and Z are each independently

5 H, fluorine, chlorine, propyl, allyl, methoxy, or CH^2SR^1 ;

and the pharmaceutically acceptable salts thereof.

Some of the compounds described herein
contain one or more centers of asymmetry and may thus
10 give rise to diastereoisomers and optical isomers.
The present invention is meant to comprehend such
possible diastereoisomers as well as their racemic
and resolved optically active forms.

Tables 1-4 list compounds of Formula I of
15 this invention.

20

25

30

TABLE I
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
2	CH ₃	H	4-OOC ₂ CH ₃	O	H	H	-	-	-
4	CH ₃	H	4-OH	O	5-allyl	H	-	-	-
5	CH ₃	H	4-OH	O	5-propyl	H	-	-	-
6	CH ₃	H	4-OOC ₂ CH ₃	O	5-propyl	H	-	-	-
7	CH ₃	H	4-OH	O	7-propyl	H	-	-	-
8	CH ₃	C ₂ H ₅	4-OH	O	5-allyl	H	-	-	-
9	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	H	H	H
10	C ₃ H ₇	H	4-OH	O	H	H	-	-	-
11	C ₃ H ₇	H	4-allyl	O	H	H	-	-	-
12	C ₃ H ₇	H	4-OH	O	5-allyl	H	-	-	-
13	C ₆ H ₅	H	4-OH	O	H	H	-	-	-
14	CH ₃	CH ₂ 4-pyrrolyl	4-OH	O	5-propyl	H	H	H	H
15	CH ₃	CH ₂ C ₆ H ₅	5-OH	O	6-OH	H	H	H	H
16	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OH	H	H
17	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H
21	CH ₃	H	5,6-OCH ₂ O	O	H	H	-	-	-
22	CH ₃	H	4-OCH ₃	O	7-propyl	H	-	-	-
24	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	O	5-propyl	H	4-OH	H	H

TABLE I (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
25	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ CH ₃	O	5-propyl	H	4-OCH ₃	H	H
26	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	H	H	H
27	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-OH	H	H
28	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-OCH ₃	H	H
29	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-F	H	H
30	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-Cl	H	H
31	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-N(CH ₃) ₂	H	H
32	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-F	H	H
33	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-Cl	H	H
34	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-N(CH ₃) ₂	H	H
35	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	H	H	H
36	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-F	H	H
37	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-OH	H	H
38	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-OCH ₃	H	H
39	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-F	4-N(CH ₃) ₂	H	H
40	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H

TABLE I (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
41	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OH	H	H
42	C ₃ H ₇	CH ₂ C ₆ H ₅	5-OH	O	6-OH	H	4-OCH ₃	H	H
43	C ₃ H ₇	CH ₂ C ₆ H ₅	5-OH	O	6-OH	H	4-F	H	H
44	CH ₃	CH ₂ C ₆ H ₅	5-OH	O	H	H	4-OCH ₃	H	H
45	CH ₃	CH ₂ C ₆ H ₅	6-OH	O	5-propyl	H	4-OCH ₃	H	H
46	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-allyl	H	4-OCH ₃	H	H
48	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OH ₂ SO ₃	H	4-OCH ₃	H	H
49	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OH ₂ CO ₃	H	H	H	H
50	CH ₃	CH ₂ 6-quinoline	4-OH	O	5-propyl	H	H	H	H
51	CH ₃	CH ₂ 3-furan	4-OH	O	5-propyl	H	H	H	H
52	CH ₃	CH ₂ 3-thiophene	4-OH	O	5-propyl	H	H	H	H
53	CH ₃	CH ₂ 3-pyrrole	4-OH	O	5-propyl	H	H	H	H
54	CH ₃	CH ₂ 2-pyridyl	4-OH	O	5-propyl	H	H	H	H
55	CH ₃	CH ₂ -thiadiazole	4-OH	O	5-propyl	H	H	H	H
56	CH ₃	CH ₂ thiazole	4-OH	O	5-propyl	H	H	H	H
57	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H

TABLE I (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
58	CH ₃	C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H
59	CH ₃	C ₆ H ₅	4-OH	O	5-propyl	H	4-OH	H	H
60	CH ₃	C ₆ H ₅	4-OH	O	5-propyl	H	4-F	H	H
61	CH ₃	C ₆ H ₅	4-OH	S	5-propyl	H	4-OCH ₃	H	H
62	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	H	H	H	H
63	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	H	4-OCH ₃	H	H
64	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	7-F	4-OCH ₃	H	H
65	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	7-F	4-F	H	H
66	CH ₃	CH ₂ C ₆ H ₅	5-OH	S	6-OH	H	4-OCH ₃	H	H
67	CH ₃	CH ₂ C ₆ H ₅	4-OH	SO	5-propyl	7-F	4-OCH ₃	H	H
68	CH ₃	CH ₂ C ₆ H ₅	4-OH	SO ₂	5-propyl	7-F	4-OCH ₃	H	H
69	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OCH ₃	7-F	4-OCH ₃	H	H
70	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OCH ₃	7-F	4-OCH ₃	H	H
72	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	H	H	4-Cl	H	H
73	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OCH ₃	3-CHO	H
74	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-Br	H	H
75	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-Cl	H	H

TABLE I (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
76	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	7-Cl	4-F	H	H
77	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OAc	H	H
78	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	H	4-OH	H	H
79	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OH	H	H
80	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	H	H	4-OH	H	H
81	CH ₃	CH ₂ C ₆ H ₅	7-OH	0	H	H	4-OCH ₃	H	H
82	CH ₃	CH ₂ C ₆ H ₅	4-allyl	0	H	H	4-OCH ₃	H	H
84	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OCH ₃	H	H
85	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-F	4-OCH ₃	H	H
86	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
87	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₂ CH ₃	0	5-propyl	7-F	4-OCH ₃	H	H
88	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
89	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Br	4-OCH ₃	H	H
90	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
91	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-allyl	H	4-OCH ₃	H	H
92	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H

TABLE I (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
93	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	7-propyl	H	4-OCH ₃	H	H
94	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-OH	4-OCH ₃	H	H
95	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Pr	4-OCH ₃	H	H
96	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-Cl	7-Pr	4-OCH ₃	H	H
97	CH ₃	CH ₂ C ₆ H ₅	4-OP(O) ₂ H ₂	0	5-propyl	7-Cl	4-OCH ₃	H	H
98	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	5-propyl	7-F	4-OCH ₃	H	H
99	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	5-propyl	7-Cl	4-OCH ₃	H	H
100	CH ₃	CH ₂ C ₆ H ₅	5-OAc	0	4-propyl	H	4-OCH ₃	H	H
101	CH ₃	CH ₂ C ₆ H ₅	5-OOC ₂ CH ₃	0	4-propyl	H	4-OCH ₃	H	H
102	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OCH ₃	H	H
103	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ Et	H	H
105	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ H	H	H
107	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	H	H	H
108	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	H	H	H
109	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OH	H	H

TABLE I (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
110	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H
111	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H
112	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
113	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
114	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
115	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
116	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
117	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
118	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
119	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
120	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
121	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
122	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
123	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
124	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-F	4-OCH ₃	H	H
125	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-F	4-OCH ₃	H	H

TABLE 1 (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
126	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
127	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
128	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
129	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
130	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₂	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
131	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₂	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
132	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
133	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
134	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
135	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
136	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
137	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
138	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₂	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
139	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₂	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
140	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-CO ₂ H	4-OCH ₃	H	H
141	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-CO ₂ H	H	H

TABLE 1 (continued)
COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
142	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-CO ₂ H	H	H
143	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CHOHCH ₂ OH	7-Cl	4-CO ₂ H	H	H
144	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CHOHCH ₂ OH	7-F	4-CO ₂ H	H	H
145	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CHOHCH ₃	7-Cl	4-CO ₂ H	H	H
146	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CHOHCH ₃	7-F	4-CO ₂ H	H	H
147	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-SO ₃ H	4-CO ₂ H	H	H
148	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH ₂ OH	7-Cl	4-CO ₂ H	H	H
149	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-C(CH ₃) ₃	7-Cl	4-CO ₂ H	H	H
150	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-C(CH ₃) ₃	7-CH ₃	4-CO ₂ H	H	H
151	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-Cl	4-CH ₃	H	H
152	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-CH ₃	4-CH ₃	H	H
153	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-F	4-CH ₃	H	H
154	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	H	4-CH ₃	H	H
155	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-Pr	4-CH ₃	H	H
156	CH ₃	CH ₂ tetrazol	5-OH	0	5-propyl	7-Pr	4-CH ₃	H	H
157	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	H	H	H	H	H

0165810

- 20 -

171411A

TABLE 1 (continued)

COMPOUNDS OF FORMULA I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
158	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	H	H	H	H	H
159	CH(CH ₃) ₂	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-CH ₃	H	H
160	CH(CH ₃) ₂	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-CH ₃	H	H
161	CH(CH ₃) ₂	H	5-OH	O	H	H	-	-	-
162	CH(CH ₃) ₂	H	4-OH	O	H	H	-	-	-

TABLE 2
Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
5	CH ₃	H	4-OH	0	5-propyl	H	-	-	-
8	CH ₃	C ₂ H ₅	4-OH	0	5-allyl	H	-	-	-
14	CH ₃	CH ₂ 4-pyridyl	4-OH	0	5-propyl	H	H	H	H
15	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	5-OH	H	H	H	H
16	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OH	H	H
17	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
26	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	H	H	H
27	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-OH	H	H
28	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-OCH ₃	H	H
29	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-F	H	H
30	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-Cl	H	H
32	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-F	H	H
33	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-Cl	H	H
34	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-Cl	H	H
35	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-(CH ₃) ₂	H	H
39	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	H	H	H
44	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	H	7-F	4-(CH ₃) ₂	H	H
						H	4-OCH ₃	H	H

TABLE 2 (continued)
Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	V ¹	V ²	V ³	V ⁴
46	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-allyl	H	4-OCH ₃	H	H
48	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ SOCH ₃	H	4-OCH ₃	H	H
49	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ SOCH ₃	H	H	H	H
50	CH ₃	CH ₂ 6-quinoline	4-OH	0	5-propyl	H	H	H	H
51	CH ₃	CH ₂ 3-furan	4-OH	0	5-propyl	H	H	H	H
52	CH ₃	CH ₂ 3-thiophene	4-OH	0	5-propyl	H	H	H	H
53	CH ₃	CH ₂ 3-pyrrole	4-OH	0	5-propyl	H	H	H	H
54	CH ₃	CH ₂ 2-pyridyl	4-OH	0	5-propyl	H	H	H	H
55	CH ₃	CH ₂ thiazole	4-OH	0	5-propyl	H	H	H	H
56	CH ₃	CH ₂ thiazole	4-OH	0	5-propyl	H	H	3-CHO	H
73	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
74	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-Br	H	H
75	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-Cl	H	H
76	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	7-Cl	4-F	H	H
77	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OAc	H	H
78	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OH	H	H
79	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OH	H	H
80	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	H	H	4-OH	H	H
81	CH ₃	CH ₂ C ₆ H ₅	7-OH	0	H	H	4-OCH ₃	H	H

TABLE 2 (continued)
Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
82	CH ₃	CH ₂ C ₆ H ₅	4-allyl	O	H	H	4-OCH ₃	H	H
84	CH ₃	CH ₂ C ₆ H ₅	4-OAc	O	5-propyl	7-Cl	4-OCH ₃	H	H
85	CH ₃	CH ₂ C ₆ H ₅	4-OAc	O	5-propyl	7-F	4-OCH ₃	H	H
86	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₂ CH ₃	O	5-propyl	7-Cl	4-OCH ₃	H	H
87	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	O	5-propyl	7-F	4-OCH ₃	H	H
88	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	O	5-propyl	7-Cl	4-OCH ₃	H	H
89	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Br	4-OCH ₃	H	H
90	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OCH ₃	H	H
91	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-allyl	H	4-OCH ₃	H	H
92	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	H	H	4-OCH ₃	H	H
93	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	7-propyl	H	4-OCH ₃	H	H
94	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-CH ₃	4-OCH ₃	H	H
95	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Pr	4-OCH ₃	H	H
96	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-Cl	7-Pr	4-OCH ₃	H	H
97	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OCH ₃	H	H
98	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₂ CO ₂ H	O	5-propyl	7-F	4-OCH ₃	H	H
99	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₂ CO ₂ H	O	5-propyl	7-Cl	4-OCH ₃	H	H
100	CH ₃	CH ₂ C ₆ H ₅	5-OAc	O	4-propyl	H	4-OCH ₃	H	H
101	CH ₃	CH ₂ C ₆ H ₅	5-OOC ₂ CH ₃	O	4-propyl	H	4-OCH ₃	H	H

TABLE 2 (continued)
Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	V ¹	V ²	V ³	V ⁴
102	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OCH ₃	H	H
103	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ Et	H	H
105	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ H	H	H
107	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	H	H	H
108	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	H	H	H
110	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OAc	0	H	H	4-OCH ₃	H	H
111	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H
112	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
113	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
113	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
114	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ H	0	5-propyl	7-Cl	4-OCH ₃	H	H
115	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
116	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₃ H	7-Cl	4-OCH ₃	H	H
117	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₃ H	7-Cl	4-OCH ₃	H	H
118	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
119	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₃ H	7-Cl	4-OCH ₃	H	H
120	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ H	0	CH ₂ SO ₃ H	7-Cl	4-OCH ₃	H	H
121	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₂ CO ₂ H	0	CH ₂ SO ₃ H	7-Cl	4-OCH ₃	H	H
122	CH ₃	CH ₂ C ₆ H ₅	4-OPO ₃ H ₂	0	CH ₂ SO ₃ H	7-F	4-OCH ₃	H	H

TABLE 2 (continued)
Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
123	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₃ 2	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H
132	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOH ₃	7-Pr	4-OCH ₃	H	H
133	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Pr	4-OCH ₃	H	H
134	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
135	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Pr	4-OCH ₃	H	H
136	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₃ H	0	CH ₂ SOH ₃	7-Pr	4-OCH ₃	H	H
137	CH ₃	CH ₂ C ₆ H ₅	4-OOCH ₂ CH ₂ CO ₂ H	0	CH ₂ SOH ₃	7-Pr	4-OCH ₃	H	H
138	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₃ 2	0	CH ₂ SOH ₃	7-Pr	4-OCH ₃	H	H
139	CH ₃	CH ₂ C ₆ H ₅	4-OPH ₃ 2	0	CH ₂ SO ₂ CH ₃	7-Pr	4-OCH ₃	H	H
140	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-CO ₂ H	4-OCH ₃	H	H
141	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-CO ₂ H	H	H
142	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-CO ₂ H	H	H
143	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ COOHCH ₂ OH	7-Cl	4-CO ₂ H	H	H
144	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ COOHCH ₂ OH	7-F	4-CO ₂ H	H	H
145	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ COOHCH ₃	7-Cl	4-CO ₂ H	H	H
146	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ COOHCH ₃	7-F	4-CO ₂ H	H	H
147	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-SO ₃ H	4-OCH ₃	H	H
148	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH ₂ OH	7-Cl	4-CO ₂ H	H	H
149	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-C(CH ₃) ₃	7-Cl	4-CO ₂ H	H	H

TABLE 2 (continued)
Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
152	CH ₃	CH ₂ tetrazol	4-OH	O	5-propyl	7-Cl	4-CH ₃ O	H	H
153	CH ₃	CH ₂ tetrazol	4-OH	O	5-propyl	7-F	4-CH ₃ O	H	H
154	CH ₃	CH ₂ tetrazol	4-OH	O	5-propyl	H	4-CH ₃ O	H	H
157	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	H	H	H	H	H
158	CH ₃	CH ₂ C ₆ H ₅	4-OAc	O	H	H	H	H	H
161	CH(CH ₃) ₂	H	5-OH	O	H	H	-	-	-
162	CH(CH ₃) ₂	H	4-OH	O	H	H	-	-	-

TABLE 3
More-Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
8	CH ₃	C ₂ H ₅	4-OH	0	5-allyl	H	-	-	-
14	CH ₃	CH ₂ -4-pyridyl	4-OH	0	5-propyl	H	H	H	H
15	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	6-OH	H	H	H	H
16	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OH	H	H
17	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
33	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-Cl	H	H
38	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-OCH ₃	H	H
72	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	3-CHO	H
74	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-Br	H	H
75	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	H	H	H
76	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	7-Cl	4-F	H	H
77	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OH	H	H
78	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OH	H	H
79	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OH	H	H
80	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	H	H	4-OH	H	H
81	CH ₃	CH ₂ C ₆ H ₅	7-OH	0	H	H	4-OCH ₃	H	H
82	CH ₃	CH ₂ C ₆ H ₅	4-allyl	0	H	H	4-OCH ₃	H	H
84	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H

TABLE 3 (continued)
 More-Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
85	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-F	4-OCH ₃	H	H
86	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
87	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	0	5-propyl	7-F	4-OCH ₃	H	H
88	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
89	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Br	4-OCH ₃	H	H
90	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
91	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-allyl	H	4-OCH ₃	H	H
92	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H
93	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	7-propyl	H	4-OCH ₃	H	H
94	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-CH ₃	4-OCH ₃	H	H
95	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Pr	4-OCH ₃	H	H
96	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-Cl	7-Pr	4-OCH ₃	H	H
97	CH ₃	CH ₂ C ₆ H ₅	4-OC ₂ H ₅	0	5-propyl	7-Cl	4-OCH ₃	H	H
98	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	5-propyl	7-F	4-OCH ₃	H	H
99	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	5-propyl	7-Cl	4-OCH ₃	H	H
100	CH ₃	CH ₂ C ₆ H ₅	5-OAc	0	4-propyl	H	4-OCH ₃	H	H
101	CH ₃	CH ₂ C ₆ H ₅	5-OOC ₂ CH ₃	0	4-propyl	H	4-OCH ₃	H	H
102	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OCH ₃	H	H
103	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ Et	H	H

TABLE 3 (continued)
More-Preferred Compounds of Formula I

	R ¹	R ²	R ³	X	Y	V ¹	V ²	V ³	V ⁴
104	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CO ₂ Et	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ Et	H	H
105	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₂ CO ₂ H	H	H
109	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OH	H	H
110	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OMe	0	H	H	4-OCH ₃	H	H
111	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H
112	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
113	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
114	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₃ H	0	5-propyl	7-Cl	4-OCH ₃	H	H
157	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	H	H	H	H	H

TABLE 4
Most-Preferred Compounds of Formula I

	1	2	3	X	Y	Y ¹	Y ²	Y ³	Y ⁴
14	CH ₃	CH ₂ 4-pyridyl	4-OH	0	5-propyl	H	H	H	H
16	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OH	H	H
17	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
38	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-OCH ₃	H	H
77	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OAc	H	H
78	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	H	4-OH	H	H
84	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OCH ₃	H	H
85	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-F	4-OCH ₃	H	H
86	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH(CH ₃) ₂	0	5-propyl	7-Cl	4-OCH ₃	H	H
87	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₃	0	5-propyl	7-F	4-OCH ₃	H	H
88	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
90	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
94	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-CH ₃	4-OCH ₃	H	H
95	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Pr	4-OCH ₃	H	H
97	CH ₃	CH ₂ C ₆ H ₅	4-OP(O) ₂ H ₂	0	5-propyl	7-Cl	4-OCH ₃	H	H
98	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₂ CO ₂ H	0	5-propyl	7-F	4-OCH ₃	H	H
99	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₂ CH ₂ CO ₂ H	0	5-propyl	7-Cl	4-OCH ₃	H	H
100	CH ₃	CH ₂ C ₆ H ₅	5-OAc	0	4-propyl	H	4-OCH ₃	H	H
101	CH ₃	CH ₂ C ₆ H ₅	5-OCH ₂ CH ₃	0	4-propyl	H	4-OCH ₃	H	H

TABLE 4 (continued)
Most-Preferred Compounds of Formula I

	1 R	2 R	3 R	X	Y	Y ¹	Y ²	Y ³	Y ⁴
102	CH ₃	CH ₂ C ₆ H ₅	5-OH	O	4-propyl	H	4-OCH ₃	H	H
103	CH ₃	CH ₂ C ₆ H ₅	4-OMe	O	5-propyl	7-Cl	4-OCH ₂ CO ₂ Et	H	H
105	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OCH ₂ CO ₂ H	H	H
109	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OH	H	H
112	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OCH ₃	H	H
113	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H
114	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₃ H	O	5-propyl	7-Cl	4-OCH ₃	H	H
157	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	H	H	H	H	H

2882P/1041A

2884P/1045A

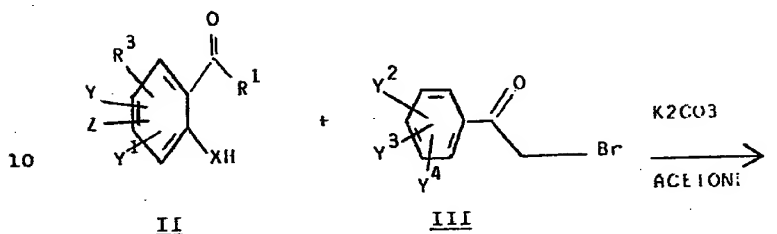
- 32 -

171411A

The following reaction schemes illustrate
the preparation of compounds of the present invention:

SCHEME I

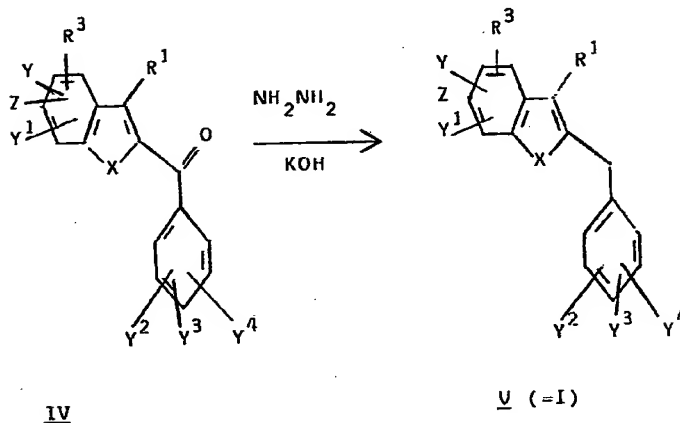
5



15

20

25



30

A suitable acetophenone (II) wherein Y is as defined above is reacted with a substituted phenacyl bromide (III) wherein Y is as defined above at a temperature ranging from room temperature to about 150°C in an inert solvent (preferably at reflux in acetone) in the presence of a base (for example, an

2882P/1043A

2884P/1045A

- 33 -

171411A

alkali metal hydroxide or carbonate) to give the corresponding benzoyl benzofuran derivative (IV). The compound of the formula IV is then reduced to give the compound of Formula I. For example,

5 subsequent treatment of IV with hydrazine and a strong base at a temperature of about 150 to 210°C preferably using the Huang Minlon modification of Wolff-Kishner conditions (J. Am. Chem. Soc. 68, 2487 (1946)) yields the desired benzyl benzofuran

10 derivative I. Alternatively, compound IV can be reduced to compound I using the zinc amalgam and a strong acid (preferably hydrochloric acid). See, for example, Ber. 46, 1837 (1913). Alternatively,

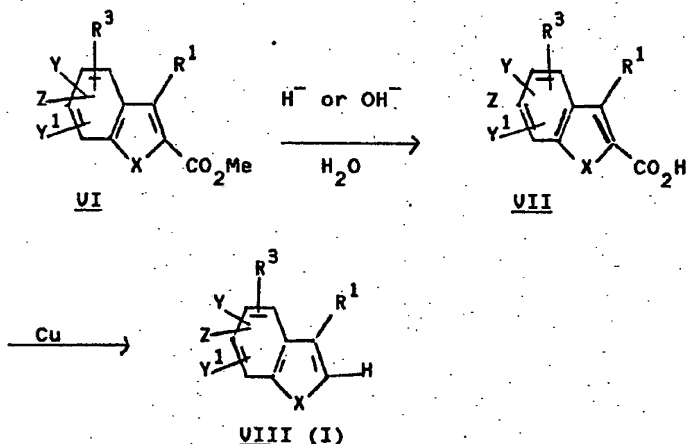
15 compound IV can be reduced to compound I using a mixture of lithium aluminum hydride and aluminum chloride in ether or tetrahydrofuran as solvent at a temperature range varying from 0°C to 65°C.

SCHEME II

20

25

30



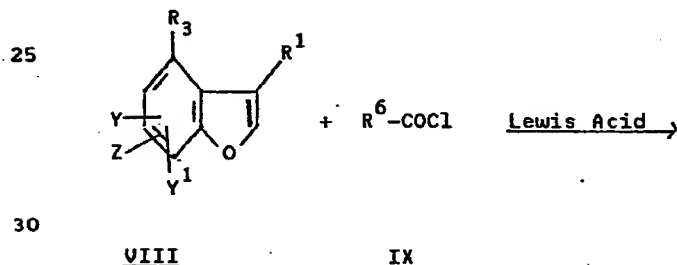
2882P/1043A

2884P/1045A

- 34 -

171411A

According to the method of Scheme II, hydrolysis of an appropriate compound of the formula VI, wherein Y is as defined above, with a strong acid and/or a strong base in water, or a mixture of water and a water soluble solvent, at a temperature ranging from room temperature to reflux (preferably, reflux) yields the corresponding acid of formula VII. Compounds of the formula VI are disclosed in U.S. Serial Number 661,645, filed October 17, 1984 (Attorney Docket Number 169601A), the disclosure of which is hereby incorporated herein by reference. The acid of formula VII is then decarboxylated to yield the corresponding benzofuran derivative of the formula VIII. This may be done by heating the acid in quinoline in the presence of copper. It can also be done by heating at reflux compound VII with a strong acid such as hydrochloric acid in a two-phase system made up of toluene and aqueous acid. Benzene or xylene or other aromatic hydrocarbons can be substituted for toluene.

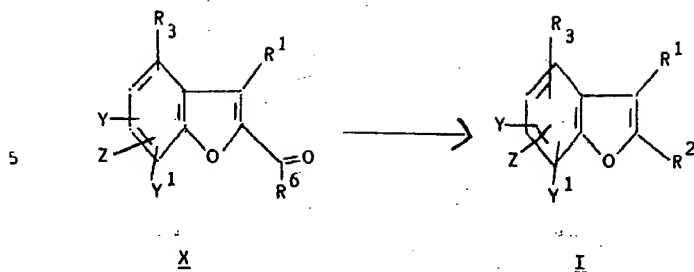
SCHEME III

2882P/1047A

2884P/1045A

35 -

171411A



10 wherein R^6 is C_1 to C_5 alkyl, $(CH_2)_{n-1}Het$, or
 - $(CH_2)_{n-1}PhY_2Y_3Y_4$.

Following Scheme III, Compound VIII, which is unsubstituted in position 2, can be reacted with
 15 an acid halide IX in the presence of a Lewis acid. Preferably aluminum chloride, to yield the 2-acyl derivative X. This reaction is best carried out in a solvent such as methylene chloride or ethylene dichloride at a temperature ranging from 0° to 25°C.
 20 The compound of the Formula X is then reduced to give the compound of Formula I. For example, subsequent treatment of X with hydrazine and a strong base at a temperature of about 150 to 210°C using the Huang-Minlon modification of Wolff-Kishner conditions
 25 (J. Am. Chem. Soc. 68, 2487 (1946)) yields the desired alkyl benzofuran derivative I. Alternatively, compound X can be reduced to compound I using the zinc amalgam and a strong acid (preferably hydrochloric-acid). See, for example,
 30 Bev., 46, 1837 (1913).

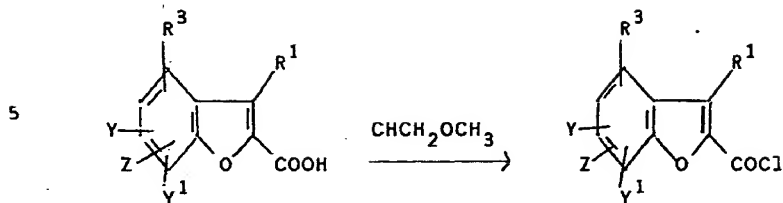
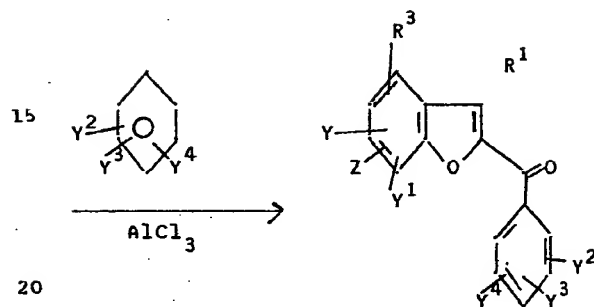
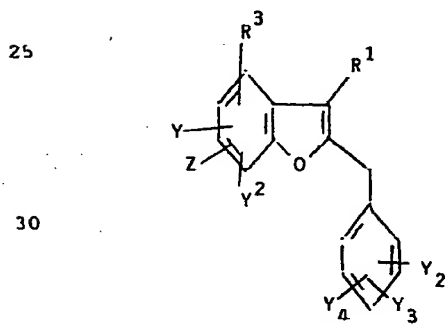
Alternatively, compound X can be reduced to compound I using a mixture of lithium aluminum hydride and aluminum chloride in ether or tetrahydrofuran as solvent at a temperature range varying from 0° to 65°C.

2882P/1043A

2884P/1045A

36 -

171411A

SCHEME IVVIIXIIVV (I)

2882P/1043A

2884P/1045A

- 37 -

171411A

Scheme IV describes another synthesis of compounds of Formula I. A carboxylic acid derivative VII is reacted with dichloromethyl methyl ether at reflux for 30 minutes to 2 hours to yield the corresponding acid chloride XI. This acid chloride XI can then be reacted with a suitably substituted aromatic derivative such as anisole, toluene, or the like to yield the desired 2-benzoyl derivative IV. The Friedel-Crafts acylation reaction is best carried out in an inert solvent such as methylene chloride or ethylene dichloride and is catalyzed very efficiently by a Lewis acid, preferably aluminum chloride. The 2-benzoyl derivative IV is then reduced to the 2-benzyl derivative V. For example, subsequent treatment of IV with hydrazine and a strong base at a temperature of about 150 to 210°C preferably using the Huang Minlon modification of Wolff-Kishner conditions (J. Am. Chem. Soc. 68, 2487 (1946)) yields the desired benzyl benzofuran derivative V. Alternatively, compound IV can be reduced to compound V using the zinc amalgam and a strong acid (preferably hydrochloric acid). See, for example, Ber. 46, 1837 (1913). Alternatively, compound IV can be reduced to compound V using a mixture of lithium aluminum hydride and aluminum chloride in ether or tetrahydrofuran as solvent at a temperature range varying from 0°C to 65°C.

In those instances when asymmetric centers are present, more than one stereoisomer is possible, and all possible isomeric forms are deemed to be included within the planar structural representations shown. Optically active (R) and (S) isomers may be resolved using conventional techniques known to the skilled artisan.

2882P/1043A

2884P/1045A

- 38 -

171411A

The compounds of Formula I may be tested using one or more of the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity and other relevant activities.

5

RBL-1 5-Lipoxygenase

Rat basophilic leukemia (RBL-1) cells are sonicated and centrifuged at 125000 xg. The resulting supernatant fraction is incubated with
10 arachidonic acid (labelled with ^{14}C) to convert a portion of it to ^{14}C -5(S)-hydroxyicosatetraenoic acid (5-HETE). Compounds being evaluated as inhibitors of 5-Lipoxygenase are added prior to the addition of arachidonic acid. 5-HETE is isolated by
15 extraction and paper chromatography, and quantitated by determining the amount of radioactivity (cpm) associated with 5-HETE.

Reference: Egan, R.W.; Tischler, A.M.; Baptista, E. H.; Ham, E. A.; Soderman, D.D.; and
20 Gale, P.H.; Advances in Prostaglandin, Thromboxane and Leukotriene Research, 11, 151, (1983), (Samuelsson, B.; Ramwell, P.W.; and Paoletti, R.; (eds.), Raven Press, N.Y.

25

Mouse Macrophage Assay

Mouse peritoneal macrophages are treated sequentially with arachidonic acid (labelled with tritium); the compound being evaluated as an inhibitor, and a stimulator (zymosan). Metabolites
30 derived from arachidonic acid (PGE_2 , 6-keto PG-F_{1a} and leukotriene C_4) are separated from the incubation medium by extraction and chromatography, and then quantitated by determining the amount of

2882P/1043A

2884P/1045A

- 39 -

171411A

radioactivity (cpm) associated with each of them. Inhibitors cause a reduction in the amount of radioactivity (cpm) associated with a given metabolite. (This protocol is identical to that described in the reference except that the radioactivity herein associated with the LTC₄ is determined by counting an aliquot of the final aqueous solution directly rather than chromatographing it first.

- 10 Reference: Humes, J.L. et al., J. Biol. Chem., 257, 1591-4, (1982).

Rat Polymorphonuclear Leukocyte

(P.M.N.) Assay

- 15 Rats under ether anesthesia are injected (intraperitoneally) with 8 ml of a suspension of sodium caseinate (6 grams in about 50 ml water). After 15 to 24 hours the rats are sacrificed (CO₂) and the cells from the peritoneal cavity are
- 20 recovered by lavage with 20 ml of buffer (Eagles Minimal Essential Medium containing 30 mM HERPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous shaking, filtered through lens paper,
- 25 recentrifuged and finally suspended in buffer at a concentration of 10 cells/ml. A 500 µl aliquot of the suspension (PMN) and test compound are preincubated for 2 minutes at 37°C, followed by the addition of 10 µM A-23187 calcium ionophore
- 30 (Calbiochem). The suspension is stirred for an additional 4 minutes then bioassayed for LTB₄ content by adding an aliquot to a second 500 µl portion of the PMN at 37°C. The LTB₄ produced in

2882P/1043A

2884P/1045A

- 40 -

171411A

the first incubation causes aggregation of the second PMN, is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually -70%) for the untreated control. The percentage inhibition of LTB₄ formation is calculated from the ratio of transmission change in the sample to the transmission change in the compound-free control.

10

Antigen Challenge 'in vitro' Assay

Male guinea pigs weighing 300-350 g are sensitized by injecting (intraperitoneally) 0.5 ml of a suspension containing 0.4 mg of egg albumin (Ovalbumin, Grade V, Sigma Chemical Co.) and 4.0 g aluminum hydroxide in 19.6 ml of saline. Two weeks are permitted for sensitization to occur.

Three sensitized guinea pigs are stunned and exanguinated. The tracheas are removed, freed of adhering tissue and divided longitudinally by cutting through the cartilaginous tissue directly opposite the muscle insertion. Each opened trachea is then transected between every second cartilage. Four of the cut sections are tied together, end to end, in a series with No.7 silk thread ensuring that the tracheal muscles are all in the same vertical plane. Thus, each chain consists of tissue from three different animals.

The chain so formed is then suspended under 1 g of tension (by silk ties at each end) in a 20 ml organ bath containing 10 ml of modified¹ Krebs-Henseleit buffer solution gassed with 95% O₂ and 5% CO₂ at 37°C. Mepyramine (0.55 µg/ml) and indomethacin (2.67 µg/ml) are added to the buffer to

2882P/1043A

2884P/1045A

- 41 -

171411A

avoid the contribution of histamine receptors and cyclooxygenase products to the contraction. To record responses one end of the tracheal chain is attached to a Gould-Statham UC-2 force displacement transducer which is connected to a Beckman Type R-dynograph. The preparations are allowed to equilibrate for one hour during which time the tissues are automatically washed (10 ml volume displacement) every 6 minutes.

10

¹ modified Krebs solution in grams/liter and (mM):

NaCl - 6.87 (120); glucose - 2.1 (11); NaHCO₃ - 2.1 (25); KCl - 0.32 (4.72); CaCl₂ - 0.28 (2.5);

15

MgSO₄·7H₂O - 0.11 (0.5); KH₂PO₄ - 0.16 (1.2); pH at bathing solution = 7.35 ± 0.05.

20

After the equilibration period the tissues are primed with methacholine (3 µg/ml; 1.5 x 10⁻⁵M), washed and allowed to recover to baseline. The tissues are treated again with a second dose of methacholine, washed, allowed to return to baseline and washed for an additional hour.

25

Two chains are used as a control. These are incubated in a concentration of egg albumin sufficient to induce an average contraction of 50-80% of the methacholine response.

30

Each compound to be tested is added to two their baths (at a final concentration in each bath of 10 µg/ml) 15 minutes prior to challenging the fresh chains with egg albumin.

2882P/1043A

2884P/1045A

- 42 -

171411A

5 The response of the challenged tissue is expressed as a percentage of the methacholine maximum. The percentage inhibition for each compound is then calculated. Compounds which at 10 µg/ml (final concentration) inhibit the egg albumin response by 50% or more are retested at a lower concentration.

Asthmatic Rat Assay

10 Rats are obtained from an inbred line of asthmatic rats. Both female and male rats from 200 to 300 g are used.

15 Egg albumin (EA), grade V, crystallized and lyophilized, is obtained from Sigma Chemical Co., St. Louis. Bordetella pertussis vaccine, containing 30×10^9 killed bacteria per ml is obtained from the Institute Armand-Frappier, Laval des Rapides, Quebec. Aluminum hydroxide is obtained from the Regis Chemical Company, Chicago.

20 The challenge and subsequent respiratory recordings are carried out in a clear plastic box with internal dimensions 10 x 6 x 4 inches. The top of the box is removable; in use, it is held firmly in place by four clamps and an airtight seal is maintained by a soft rubber gasket. Through the center of each end of the chamber a Devilbiss nebulizer (No. 40) is inserted via an airtight seal and each end of the box also has an outlet. A Fleisch No. 0000 pneumotachograph is inserted into one end of the box and coupled to a Grass volumetric pressure transducer (PT5-A) which is then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the

25

30

2882P/1043A

2884P/1045A

- 43 -

171411A

outlets are open and the pneumotachograph is isolated from the chamber. The outlets are closed and the pneumotachograph and the chamber are connected during the recording of the respiratory patterns. For challenge, 2 ml of a 3% solution of antigen in saline is placed into each nebulizer and the aerosol is generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minute.

- Rats are sensitized by injecting (subcutaneously) 1 ml of a suspension containing 1 mg EA and 200 mg aluminum hydroxide in saline. Simultaneously, they receive an injection (intraperitoneally) of 0.5 ml of B. pertussis vaccine. They are used between days 14 and 18 postsensitization. In order to eliminate the serotonin component of the response, rats are pretreated intravenously 5 minutes prior to aerosol challenge with 30 gm/kg methylserzide. Rats are then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their respiratory profiles are recorded for a further 25 to 30 minutes. The duration of continuous dyspnoea is measured from the respiratory recordings.

- Compounds are generally administered either intraperitoneally 1 hour prior to challenge or orally 1 and 1/2 hours prior to challenge. They are either dissolved in dimethylsulfoxide or suspended in 0.1% methocel and 0.5% Tween 80. The volume injected is 2 ml/kg (intraperitoneally) or 10 ml/kg (orally). Prior to oral treatment rats are starved overnight. Their activity is determined in terms of their ability to decrease the duration of symptoms of dyspnoea in comparison with a group of vehicle-

2882P/1043A

2884P/1045A

- 44 -

171411A

treated controls. Usually, a compound is evaluated at a series of doses and an ED_{50} is determined. This is defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

5

PAF-Induced Hyperalgesia Assay

Female Sprague-Dawley rats, 35 to 40 g are fasted overnight. Platelet activating factor, PAF, (L-lecithin B-acetyl O-alkyl) 1 μ g/0.1 ml is given by subplantar injection in the rat paw. The compounds to be evaluated are homogenized in Aqueous Vehicle (0.9% benzyl alcohol, 0.5% Tween 80 and 0.4% methylcellulose) and administered orally in a volume of 0.1 ml, 30 minutes prior to PAF.

15

Animals are tested 1, 2, 3 and 4 hours after PAF administration. The vocalization threshold, defined as the pressure (mmHg) needed to evoke a squeak response, was recorded for both the injected and contralateral paw. No animal is subjected to pressure greater than 60 mmHg. Hyperalgesia is defined as a decrease in vocalization threshold as compared to a normal paw. Percent inhibition of hyperalgesia is calculated as the proportion of animals with vocalization thresholds greater than 200% of controls.

20

25

Brewer's Yeast Hyperalgesia Assay

The standard method [Winter, C.A. et al., J. Pharm. Exp. Ther. 150, 165-171 (1965)] for yeast hyperalgesia is used. Female Sprague-Dawley rats, 35-40 g are fasted overnight. A 5% solution (volume 0.1 ml) of Brewer's yeast is injected into the rat paw. The compound is homogenized in aqueous vehicle

30

2882P/1043A

2884P/1045A

- 45 -

17141IA

and given orally 2 hours after yeast. Vocalization thresholds are recorded 1 hour after drug (3 hours after yeast). Percent inhibition of hyperalgesia is determined by the proportion of animals with
5 vocalization thresholds greater than 25 mmHg.

The compounds of the Formula I have unexpected activity as inhibitors of the mammalian biosynthesis of leukotriene B_4 , as well as leukotrienes C_4 , D_4 , E_4 and F_4 , the active
10 elements of the slow reacting substance of anaphylaxis (SRS-A). The compounds of Formula I act as inhibitors of the mammalian 5-lipoxygenase enzyme system of the arachidonic acid cascade. This inhibition of the mammalian biosynthesis of
15 leukotrienes indicates that the compositions are useful to treat, prevent or ameliorate, in mammals and especially in humans 1) pulmonary conditions including diseases such as asthma, 2) allergies and allergic reactions such as allergic rhinitis,
20 contact dermatitis, allergic conjunctivitis and the like, 3) inflammation such as arthritis, 4) pain, 5) skin conditions such as psoriasis and the like, and 6) cardiovascular conditions such as angina and the like, and that the compounds are cytoprotective
25 agents.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive gastritis; erosive esophagitis; inflammatory bowel
30 disease; ethanol-induced hemorrhagic erosions; hepatic ischemia; noxious agent induced damage or necrosis of hepatic, pancreatic, renal, or myocardial

2882P/1043A

2884P/1045A

- 46 -

171411A

tissue, liver parenchymal damage caused by hepatotoxic agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage, bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure.

The cytoprotective activity of a compound may be observed in both animal and man by noting the increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids, strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are: (A) an ethanol-induced lesion assay and (B) an indomethacin-induced ulcer assay.

A. Ethanol-Induced Gastric Ulcer Assay

Twenty-four hour fasted Sprague-Dawley (S.D.) rats are perorally (p.o.) dosed with 1.0 ml absolute ethanol. Fifteen to thirty minutes prior to ethanol administration, groups of rats each receive either an aqueous vehicle (aqueous methylcellulose 5% wt.) or the test compound at various doses perorally. One hour later, the animals are sacrificed and stomach mucosa are examined for resulting lesions.

B. Indomethacin-Induced Ulcer Assay

Indomethacin, 10 mg/kg p.o., is used to induce ulcers in 24 hour fasted S. K. rats. Fifteen minutes prior to indomethacin administration, groups of rats each receive either an aqueous vehicle (5% by weight methylcellulose) or the test compound at various doses perorally. Four hours later the animals are sacrificed and stomach mucosa are examined for resulting ulcers.

10

The magnitude of a prophylactic or therapeutic dose of a compound of formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of formula I and its route of administration. When a compound of formula I is used in a pharmaceutical composition, the effective concentration in the composition will vary as required by the mode of administration, dosage form and pharmacological effect and level desired. In general, the daily dose range for anti-asthmatic, anti-allergic or anti-inflammatory use and, generally, uses other than cytoprotection lies within the range of from about 0.01 mg to about 100 mg per kg body weight of a mammal. This dosage may be administered in a single or divided individual doses. More or less of the general daily dosage may be necessary depending upon the individual needs of the patient.

20
25
30

The exact amount of a compound of the Formula I to be used as a cytoprotective agent will depend on, inter alia, whether it is being administered to heal damaged cells or to avoid future

2882P/1043A

2884P/1045A

- 48 -

171411A

- damage, on the nature of the damaged cells or to avoid future damage, on the nature of the damaged cells (e.g., gastro-intestinal ulcerations vs. nephrotic necrosis), and on the nature of the causative agent. An example of the use of a compound of the Formula I in avoiding future damage would be co-administration of a compound of the Formula I with a non-steroidal anti-inflammatory drug that might otherwise cause such damage (for example, indomethacin). For such use, the compound of Formula I is administered from 30 minutes prior up to 30 minutes after administration of the NSAID (for example, in a combination dosage form). Preferably it is administered prior to or simultaneous with the NSAID.

- The effective daily dosage level for compounds of Formulae I inducing cytoprotection in mammals, especially humans, will generally range from about 0.002 mg/kg to about 100 mg/kg, preferably from about 0.02 mg/kg to about 30 mg/kg. The dosage may be administered in single or divided doses.

- Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a leukotriene antagonist. For example, oral, rectal, transdermal, parenteral, intramuscular, intravenous and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules and the like.

- For treating pulmonary conditions such as asthma, the mode of administration may be oral, parenteral, by inhalation, by suppository and the like. Suitable oral dosage forms are tablets.

2882P/1043A

2884P/1045A

- 49 -

171411A

- elixirs, emulsions, solutions, capsules, including delayed or sustained release capsules and the like. Parenteral dosage forms include solutions, emulsions and the like. Dosage forms for administration by
- 5 inhalation including sprays, aerosols and the like. These inhalation formulations may be administered in metered doses ranging from about 0.1 μ g to about 200 μ g, administered as needed.

- For treating allergies or allergic
- 10 reactions, such as allergic conjunctivitis, allergic rhinitis and the like, the Formula I compound may be administered by any conventional mode, e.g., orally, parenterally, topically, subcutaneously, by inhalation and the like. The oral and parenteral
- 15 dosage forms are the same type as for the pulmonary treatment. The topical application dosage forms include ointments, salves, controlled release patches, emulsions, solutions, thixotropic formulations, powders, sprays and the like. For
- 20 topical application, the percent by weight active ingredient (Formula I compound) may vary from about 0.001 to about 10%.

- For treating inflammation the mode of administration may be oral, parenteral, by
- 25 suppository and the like. The various dosage forms are the same as those described above.

- For treating skin diseases such as psoriasis, atopic dermatitis and the like, oral, topical or parenteral administration is useful. For
- 30 topical application to the diseased area salves, patches, controlled release patches, emulsions, etc., are convenient dosage forms.

2882P/1043A

2884P/1045A

- 50 -

171411A

For use as an analgesic, i.e., for treating pain, any suitable mode of administration may be used, e.g., oral, parenteral, by insufflation, by suppository and the like.

- 5 For treating cardiovascular conditions such as angina pectoris, etc., any suitable mode of administration, e.g. oral, parenteral, topical, insufflation, etc. and dosage form e.g. pills, liquid formulations, controlled release capsules, controlled
- 10 release skin patches, etc. may be used.

- The pharmaceutical compositions of the present invention comprise a compound of formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically
- 15 acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic
- 20 bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived
- 25 from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as
- 30 isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine,

procaine, hydrabamine, choline, betaine, ethlenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like.

- 5 For a useful discussion of pharmaceutical salts see S. M. Berge et al., Journal of Pharmaceutical Sciences, 66, 1-19 (1977), the disclosure of which is hereby incorporated herein by reference.

- The compositions include compositions
10 suitable for oral, rectal, ophthalmic, pummonary, nasal, dermal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature an severity
15 of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

- For use where a composition for intravenous
20 administration is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use and, generally, uses other than cytoprotection is from about 0.01 mg to about 20 mg (preferably from about 0.1 mg to about 10 mg) of a
25 compound of Formula I per kg of body weight per day and for cytoprotective use from about 0.002 mg to about 100 mg (preferably from about 0.02 mg to about 30 mg and more preferably from about 0.1 mg to about 10 mg) of a compound of Formula I of body weight per
30 day. In the case where an oral composition is employed, a suitable dosage range for anti-asthmatic, anti-inflammatory or anti-allergic use and, generally, uses other than cytoprotection is from

2882P/1043A

2884P/1045A

- 52 -

171411A

about 1 to about 100 of a compound of Formula I per kg of body weight per day, preferably from about 5 mg to about 40 mg per kg and for cytoprotective use from about 0.01 mg to about 100 mg (preferably from about 0.1 mg to about 30 mg and more preferably from about 0.1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser. The preferred composition form inhalation is a powder which may be formulated as a cartridge from which the powder composition may be inhaled with the aid of a suitable device. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

In practical use, leukotriene antagonists of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques and using conventional ingredients, e.g. diluents, carriers, etc. The carrier may take a wide variety of forms depending on the form of preparation desired form administration, e.g., oral or intravenous. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, diluents, granulating agents,

2882P/1043A

2884P/1045A

- 53 -

171411A

lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

In addition to the common dosage forms set above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosures of which are incorporated herein by reference.

Dosage forms for application to treat the eye are disclosed in U.S. Patent No. 4,348,398, the disclosure of which is incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration and by inhalation in the case of asthma therapy may be presented as discrete units such as capsules, cachets or tablets each containing an predetermined amount of the active ingredient, as a powder or granules or as a solution or suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly

2882P/1043A

2884P/1045A

- 54 -

171411A

and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet
5 may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a
10 binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet
15 contains from about 25 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 25 to about 500 mg of the active ingredient.

The following are examples of representative
20 pharmaceutical dosage forms:

	<u>Injectible Suspension</u>	<u>mg/mL</u>
	Compound of Formula I	2
	Methylcellulose	5.0
	Tween 80	0.5
25	Benzyl alcohol	9.0
	Methyl paraben	1.8
	Propyl paraben	0.2
	Water for injection to a total volume of 1 ml	

2882P/1043A

2884P/1045A

- 55 -

17141IA

<u>Aerosol for Oral Inhibition</u>		<u>mg/can</u> (200 doses/can)
	Compound of Formula I	2-40
	Oleic Acid	0.2-4.0
	Trichloromonofluoro methane	5,000-8,000*
5	Dichloromonofluoro methane	15,000-12,400*
	*To a total of 20,400	

<u>Cream</u>		<u>mg/g</u>
	Compound of Formula I	1-100
10	Cetyl alcohol	130.0
	Sodium Lauryl Sulfate	15.0
	Propylene Glycol	100.0
	Methyl paraben	1.8
	Propyl paraben	1.2
15	Purified Water of sufficient quantity to make total 1 g	

<u>Ointment</u>		<u>mg/g</u>
	Compound of Formula I	1-100
20	Methyl paraben	1.8
	Propyl paraben	1.2
	Petrolatum of sufficient quantity to make total 1 g	

<u>Tablet</u>		<u>mg/tablet</u>
	Compound of Formula I	25
	Microcrystalline Cellulose	325
	Providone	14.0
	Microcrystalline Cellulose	90.0
30	Pregelatinized Starch	43.5
	Magnesium Stearate	2.5
		500

2882P/1043A

2884P/1045A

- 56 -

171411A

<u>Capsule</u>	<u>mg/capsule</u>
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	<u>1.5</u>
5	600

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

NSAIDs can be characterized into five groups:

- (1) the propionic acid derivatives;
 - (2) the acetic acid derivatives;
 - (3) the fenamic acid derivatives;
 - 30 (4) the biphenylcarboxylic acid derivatives;
- and
- (5) the oxicams
- or a pharmaceutically acceptable salt thereof.

2882P/1043A

2884P/1045A

- 57 -

171411A

The propionic acid derivatives which may be used comprise: ibuprofen, ibuprofen aluminum, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, 5 indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tiroxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Structurally related propionic acid 10 derive-tives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-\text{CH}(\text{CH}_3)\text{COOH}$ or $-\text{CH}_2\text{CH}_2\text{COOH}$ group (which optionally can be in 15 the form of a pharmaceutically acceptable salt group, e.g., $-\text{CH}(\text{CH}_3)\text{COO}^-\text{Na}^+$ or $-\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring 20 system.

The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, 25 furofenac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxpinac, and fenclozic acid. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined 30 herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-\text{CH}_2\text{COOH}$ group

2882P/1043A

2884P/1045A

- 58 -

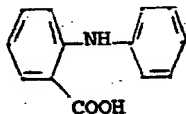
171411A

(which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

- 5 The fenamic acid derivatives which may be used comprise: mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties
10 are also intended to be encompassed by this group.

Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

15



- 20 which can bear a variety of substituents and in which the free $-\text{COOH}$ group can be in the form of a pharmaceutically acceptable salt group, e.g., $-\text{COO}^-\text{Na}^+$.

- The biphenylcarboxylic acid derivatives
25 which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

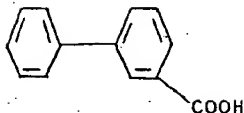
- 30 Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

2882P/1043A

2884P/1045A

59 -

171411A



5

which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO⁻Na⁺.

10

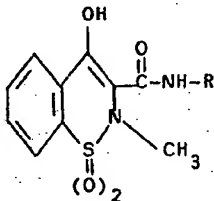
The oxicams which can be used in the present invention comprise: piroxicam, sudoxicam, isoxicam and 4-hydroxyl-1,2-benzothiazine 1,1-dioxide 4-(N-phenyl)-carboxamide. Structurally related oxicams having similar analgesic and anti-inflammatory

15

properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:

20



25

wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used:

30 acemetacin, alminoprofen, amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydanine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone,

2882P/1043A

2884P/1045A

- 60 -

17141IA

- clidanac, cloximate, dazidamine, deboxamet,
 delmetacin, detomidine, dexindoprofen, diacerein,
 di-fisalamine, difenpyramide, emorfazone, enfenamic
 acid, enolicam, epirizole, etersalate, etodolac,
 5 etofenamate, fanetizole mesylate, fenclofenac,
 fenclorac, fendosal, fenflumizole, fentiazac,
 feprazone, floctafenine, flunixin, flunoxaprofen,
 fluproquazone, fopirtoline, fosfosal, furclopofen,
 furofenac, glucametacin, guaimesal, ibuproxam,
 10 isofezolac, isonixim, isoprofen, isoxepac, isoxicam,
 lefetamine HCl, leflunomide, lofemizole, lonazolac
 calcium, lotifazole, loxoprofen, lysin clonixinate,
 meclofenamate sodium, meseclazone, miroprofen,
 nabumetone, nictindole, nimesulide, orpanoxin,
 15 oxametacin, oxapadol, oxaprozin, perisoxal citrate,
 pimeprofen, pimetacin, piroxan, pirazolac,
 pirfenidone, pirprofen, pranoprofen, proglumetacin
 maleate, proquazone, pyridoxiprofen, sudoxicam,
 suprofen, talmetacin, talniflumate, tenoxicam,
 20 thiazolinobutazone, thielavin B, tiaprofenic acid,
 tiaramide HCl, tiflamizole, timegadine, tiroxaprofen,
 tolfenamic acid, tolpadol, tryptamid, ufenamate, and
 zidometacin.

- The following NSAIDs, designated by company
 25 code number, may also be used:
 480156S, AA861, AD1491, AD1590, AFP802, AFP860,
 AHR6293, AI77B, AP504, AU8001, BAYo8276, BPPC,
 BW540C, BW755C, CHINOIN 127, CN100, CO893XX, CPP,
 D10242, DKA9, DV17, EB382, EGYT2829, EL508, F1044,
 30 FZ, GP53633, GP650, GV3658, HG/3, ITC1, ITF, ITF182,
 KB1043, KC8973, KCNTEI6090, KME4, LA2851, LT696,
 LU20884, M7074, MED15, MG18311, MR714, MR897, MY309,
 NO164, ONO3144, PR823, PV102, PV108, QZ16, R830,

2882P/1043A

2884P/1045A

- 61 -

171411A

RS2131, RU16029, RU26559, RUB265, SCR152, SH440,
SIR133, SIR136, SIR92, SPAS510, SQ27239, ST281,
SX1032, SY6001, SaH46798, TA60, TAI901, TEI615,
TVX2706, TVX960, TZI615, U60257, UR2310, WY23205,
5 WY41770, YM09561, YMI3162, YSI033, and ZK31945.

Finally, NSAIDs which may also be used
include the salicylates, specifically aspirin, and
the phenylbutazones, and pharmaceutically acceptable
salts thereof.

10 Pharmaceutical compositions comprising the
Formula I compounds may also contain inhibitors of
the biosynthesis of the leukotrienes such as are
disclosed in EP 138,481 (April 24, 1985), EP 115,394
(August 8, 1984), EP 136,893 (April 10, 1985), and EP
15 140,709 (May 8, 1985), which are hereby incorporated
herein by reference.

 The compounds of the Formula I may also be
used in combination with leukotriene antagonists such
as those disclosed in EP 106,565 (April 25, 1984) and
20 EP 104,885 (April 4, 1984) which are hereby
incorporated herein by reference and others known in
the art such as those disclosed in European Patent
Application Nos. 56,172 and 61,800; and in U.K.
Patent Specification No. 2,058,785, which are hereby
25 incorporated herein by reference.

 Pharmaceutical compositions comprising the
Formula I compounds may also contain as the second
active ingredient, antihistaminic agents such as
benadryl, dramamine, histadyl, phenergan and the
30 like. Alternatively, they may include prostaglandin
antagonists such as those disclosed in European Patent

2882P/1043A

2884P/1045A

- 62 -

171411A

Application 11,067 (May 28, 1980) or thromboxane antagonists such as those disclosed in U.S. 4,237,160. They may also contain histidine decarboxylase inhibitors such as α -fluoromethylhistidine, described in U.S. 4,325,961. The compounds of the Formula I may also be advantageously combined with an H_1 or H_2 -receptor antagonist, such as for instance cimetidine, ranitidine, terfenadine, famotidine, aminothiadiazaoles disclosed in EP 40,696 (December 2, 1981) and like compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; 4,394,508; and a pending application, U.S.S.N. 301,616, filed September 14, 1981. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Each of the references referred to in this paragraph is hereby incorporated herein by reference.

The following examples illustrate the present invention without, however, limiting the same thereto. All temperatures are in degrees Celsius.

EXAMPLE 1

4-hydroxy-2-(4-methoxybenzyl)-3-methyl-5-benzofuran

25

Step A: Preparation of 4-hydroxy-2-(4-methoxybenzyl)-3-methyl-5-propylbenzofuran

A mixture of 2,6-dihydroxy-5-propyl acetophenone (5.8 g; 30 mmoles), ω -bromo-p-methoxyacetophenone (6.8 g; 30 mmoles), anhydrous potassium carbonate (4.1 g; 30 mmoles) and acetone (150 ml) was refluxed for 22 hours. The mixture was

2882P/1043A

2884P/1045A

- 63 -

171411A

filtered and concentrated. The residue was dissolved in dichloromethane (500 ml) and extracted with 1 N sodium hydroxide (2 x 200 ml) and water (200 ml). The dichloromethane solution containing the product
5 was dried (Na_2SO_4), filtered, concentrated, and chromatographed to obtain 7.2 g of the title compound as a solid. A sample was recrystallized from 10% ethyl acetate in hexane.

m.p. 114-116°C

10 Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_4$: C, 74.05; H, 6.21.
Found: C, 74.30; H, 6.18.

Step B: Preparation of 4-hydroxy-2-(4-methoxy-
benzyl)-3-methyl-5-propylbenzofuran

15 A mixture of 4-hydroxy-2-(4-methoxy-
benzoyl)-3-methyl-5-propylbenzofuran (7.2 g; 22
mmoles), potassium hydroxide pellets (8.7 g; 155
mmoles), ethylene glycol (100 ml) and 99% hydrazine
(3.0 ml) was heated with stirring and maintaining the
20 internal temperature between 130°C and 150°C for 4
hours. The internal temperature was permitted to
rise to 175°C for 1 hour and excess water was always
allowed to escape. The mixture was cooled and poured
into excess 20% citric acid solution. The mixture
25 was extracted with ether, washed with water, dried
(Na_2SO_4), filtered, concentrated, and
chromatographed to give 4 grams of the title compound.
m.p. 83-86°C

30 Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3$: C, 77.39; H, 7.14
Found: C, 77.39; H, 7.06.

2882P/1043A

2884P/1045A

- 64 -

171411A

EXAMPLE 24-hydroxy-2-(4-hydroxybenzyl)-3-methyl-5-propyl-
benzofuran

5

Under nitrogen atmosphere, ethanethiol (4.9 g; 80 mmoles) was added dropwise over 5 minutes to a mixture of 99% sodium hydride (1.9 g; 80 mmoles) in dimethylformamide (100 ml). After stirring for 15 minutes, a solution of 4-hydroxy-2-(4-methoxybenzyl)-3-methyl-5-propylbenzofuran (2.4 g; 8 mmoles) in dimethylformamide (5 ml) was added in one portion. The mixture was refluxed for 2 hours, cooled, acidified with 20% citric acid solution and extracted with ether. The ether solution was washed with water, dried (Na_2SO_4), filtered, concentrated, and chromatographed to obtain 2.2 g of the title compound as an oil which crystallized from an ether-hexane mixture.

15

20 m.p. 117-120°C

Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_3$: C, 77.00; H, 6.80.

Found: C, 76.66; H, 7.32.

EXAMPLE 3

25

4-hydroxy-3-methyl-5-propyl-2-(4-pyridylmethyl)-
benzofuran

30

Step A: Preparation of 4-hydroxy-3-methyl-5-
propyl-2-(isonicotinoyl)-benzofuran

A mixture of 2,6-dihydroxy-5-propylaceto-phenone (5.8 g; 30 mmoles), 4-bromoacetylpyridine

2882P/1043A

2884P/1045A

- 65 -

171411A

- hydrobromide (16.8 g; 60 mmoles), anhydrous potassium carbonate (16.5 g; 120 mmoles) and acetone (200 ml) was refluxed for 22 hours. The mixture was filtered, concentrated, and chromatographed to obtain 2 g of the title compound.

m.p. 203-205°C

Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.76.

Found: C, 73.04; H, 5.88; N, 4.64.

10 Step B: Preparation of 4-hydroxy-3-methyl-5-propyl-2-(4-pyridylmethyl)-benzofuran

- A mixture of 4-hydroxy-3-methyl-5-propyl-2-(isonicotinoyl)-benzofuran (1.5 g; 5.2 mmoles), potassium hydroxide pellets (2 g; 37 mmoles), ethylene glycol (25 ml) and 99% hydrazine (0.8 ml) was heated with stirring at 130°C for 1 hour and at 155°C for 2 hours. The mixture was cooled and acidified with 20% citric acid solution. The mixture was extracted using 20% ethyl acetate in diethyl ether. The organic layer was dried (Na_2SO_4), filtered, concentrated, and chromatographed to obtain 1 g of the title compound which was then recrystallized from ethyl acetate.
- m.p. 161-163°C

25 Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.80; N, 4.97.

Found: C, 76.66; H, 7.19; N, 4.90.

EXAMPLE 4

30 2-ethyl-4-hydroxy-3-methylbenzofuran

A mixture of 2-acetyl-4-hydroxy-3-methylbenzofuran (2 g; 10.5 mmoles), potassium hydroxide

2882P/1043A

2884P/1045A

- 66 -

171411A

pellets (4 g; 73 mmoles), ethylene glycol (50 ml) and 99% hydrazine (3 ml) was heated at 100°C for 2 hours and at 180°C for 2 hours. The mixture was acidified with excess 20% citric acid solution and extracted with ether. The ether layer was dried (Na_2SO_4), filtered, concentrated, and chromatographed to obtain 1.2 g of the title compound as an oil which crystallized from hexane.

m.p. 105-107°C
10 Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$: C, 74.97; H, 6.86.
Found: C, 74.84; H, 6.76.

EXAMPLE 5

15 2-benzyl-4-hydroxy-3-methyl-5-propylbenzofuran

A mixture of 2-benzoyl-4-hydroxy-3-methyl-5-propylbenzofuran (1.2 g; 4 mmoles), potassium hydroxide pellets (1.5 g; 28 mmoles), ethylene glycol (25 ml) and 99% hydrazine (0.7 ml) was heated at 135-155°C for 3 hours. The mixture was cooled, acidified with 20% citric acid solution, extracted with ether, dried (Na_2SO_4), filtered, concentrated, and chromatographed to obtain 650 mg of the title compound as an oil which was crystallized from hexane.

m.p. 40-41°C.

Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2$: C, 81.39; H, 7.19.
Found: C, 81.46; H, 7.18.

EXAMPLE 6

5-allyl-2-ethyl-5-hydroxy-3-methylbenzofuran

5 Step A: Preparation of 4-allyloxy-2-ethyl-3-methyl-
 benzofuran

A mixture of 2-ethyl-4-hydroxy-3-methyl-benzofuran (760 mgs; 4.3 mmoles), allyl bromide (1.0 g; 8.6 mmoles), anhydrous potassium carbonate (1.1 g; 8.6 mmoles) and acetone (50 ml) was refluxed for 4 hours. The mixture was filtered, concentrated, and chromatographed to obtain 1.1 g of the title compound as an oil which was used as such in the next step.

15 Step B: Preparation of 5-allyl-2-ethyl-4-hydroxy-3-methylbenzofuran

A mixture of 4-allyloxy-2-ethyl-3-methyl-
20 benzofuran (1.0 g; 4.8 mmoles) and orthodichloro-
benzene (40 ml) was refluxed for 4 hours. The
mixture was chromatographed to obtain 1.0 g of the
title compound as an oil. The oil was recrystallized
from hexane.

25 m.p. 38-40°C

Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.45.

Found: C, 77.74; H, 7.06.

2882P/1041A

2884P/1045A

- 68 -

171411A

EXAMPLE 72-(1-(4-chlorophenyl)-vinyl)-3-methyl-benzofuran

5 To a suspension of potassium t-butoxide (448 mg; 4 mmoles) in tetrahydrofuran (25 mL) was added methyl-triphenylphosphonium bromide (1.07 gm; 3 mmoles). The mixture was stirred for a period of 2 hours. 2-(4-chlorobenzoyl)-3-methyl-4-hydroxy-
10 benzofuran (286 mg; 1 mmole) in tetrahydrofuran (5 ml) was added rapidly and the mixture was stirred for an additional 30 minutes at room temperature. The mixture was poured into 10% citric acid solution (100 ml) and was extracted with ethylacetate. The organic
15 phase was dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 10% ethylacetate in hexane to yield 210 mg (73%) of 2-(1-(4-chlorophenyl)vinyl)-3-methylbenzofuran as an oil.

20

^1H NMR 2.23 (s, 3H, CH_3), 5.57 (m, 2H, CH_2), 5.67 (s, 1H, OH), 6.43 (d of d, J = 3Hz, 9Hz, H5), 7.00 (m, 2H, H6 and H7), 7.20 (s, 4H, phenyl protons).

25

Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{ClO}_2$: C, 71.70; H, 4.60; Cl, 12.45 Found: C, 71.54; H, 4.81; Cl, 12.35.

EXAMPLE 8

30

2-(3-formyl-4-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-benzofuran

To a suspension of aluminium chloride (214 mg; 1.6 mmole) in dichloromethane (5 mL) cooled at

2882P/1043A

2884P/1045A

- 69 -

171411A

0°C was added 2-(p-methoxy-benzyl)-3-methyl-4-hydroxy-5-propyl-benzofuran (100 mg; 0.32 mmoles). A red solution resulted. To this solution was added dropwise dichloromethylmethylether (87 μ l; 0.96 mmole). There was a vigorous reaction and a color change from red to green was observed. Ice and water was then added and the mixture was extracted with ethylacetate. The organic phase was dried (Na_2SO_4), and concentrated in vacuo and the residue was chromatographed on silica gel. Elution with 10% ethylacetate in hexane yielded 40 mg (37%) of 2-(3-formyl-4-methoxybenzyl) 3-methyl-4-hydroxy-5-propyl-benzofuran.

^1H NMR 0.93 (t, 3H, J = 7Hz, CH_3), 1.60 (sextet, 2H, J = 7Hz, CH_2), 2.40 (s, 3H, CH_3), 2.63 (t, 2H, J = 7 Hz, CH_2), 3.87 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.90 (s, 1H, OH), 6.90 (s, 2H, H6 and H7), 6.93 (d, 1H, J = 9 Hz, proton ortho to methoxy), 7.40 (d of d, 1H, J = 9 Hz, 3 Hz, proton meta to methoxy), 7.73 (d, 1H, J = 3Hz, proton ortho to formyl), 10.50 (s, 1H, formyl proton).

Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_4$: C, 74.51; H, 6.55;
Found: C, 74.56; H, 6.58.

EXAMPLE 9

2-(p-chlorobenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

a) Preparation of 2-(p-chlorobenzoyl)-3-methyl-4-(chlorobenzoyloxy)-5-propyl-7-chlorobenzofuran

2882P/1043A

2884P/1045A

- 70 -

171411A

A solution of p-chlorobenzoyl chloride (3.5 gm; 20 mmoles) in ethylene dichloride (10 mL) was added slowly to a cooled suspension of aluminium chloride (5.36 gm; 40 mmoles) in ethylene dichloride (200 mL). After stirring for a period of 15 minutes, 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (1.5 gm; 7 mmoles) in ethylenedichloride (10 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 5 hours. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with 15% ethylacetate in hexane yielded 2.63 gm (75%) of 2-(p-chlorobenzoyl)-methyl-4-(p-chlorobenzoyloxy)-5-propyl-7-chlorobenzofuran, mp. 177-182°C.

20

^1H NMR 0.90 (t, $J=7$ Hz, 3H, CH_3), 1.63 (sextet, $J=7$ Hz, 2H, CH_2), 2.57 (s, 3H, CH_3), 2.63 (t, $J=7$ Hz, 2H, CH_2), 7.43 (d, $J=9$ Hz, 1H, proton ortho to chloro), 7.50 (d, $J=9$ Hz, 1H, proton ortho to chloro), 7.60 (s, 1H, H6), 8.17 (d, $J=9$ Hz, 1H, proton meta to chloro), 8.23 (d, $J=9$ Hz, 1H, proton meta to chloro).

25

b) Preparation of 2-(p-chlorobenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

30

To an ice-cold suspension of aluminium chloride (2.1 gm, 16 mmoles) in ether (300 mL) was

2882P/1043A

2884P/1045A

- 71 -

171411A

added slowly lithium aluminium hydride (2.6 gm, 68 mmoles). After stirring for a period of 10 minutes, 2-(p-chlorobenzoyl)-3-methyl-4-(p-chlorobenzoyloxy)-5-propyl-7-chlorobenzofuran (2.3 gm, 4.6 mmoles) in ether (10 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 15 minutes. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with ether. The organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with 15% ethylacetate in hexane yielded 0.30 gm (87%) of 2-(p-chlorobenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, mp. 76-77°C.

^1H NMR 0.97 (t, $J = 7$ Hz, 3H, CH_3), 1.67 (sextet, $J = 7$ Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.57 (t, $J = 7$ Hz, 2H, CH_2), 4.03 (s, 2H, CH_2), 4.80 (s, 1H, OH), 6.93 (s, 1H, H6), 7.17 (d, 2H, $J = 9$ Hz, proton ortho to chloro), 7.30 (d, $J = 9$ Hz, 1H, proton meta to chloro).

25

EXAMPLE 10

2-(p-fluorobenzyl)-3-methyl-5-propyl-4-hydroxy-benzofuran

30

a) Preparation of 2-hydroxy-5-allyloxyacetophenone

A mixture of 2,5-dihydroxyacetophenone (7.6 gm; 50 mmoles), potassium carbonate (6.9 gm; 50

2882P/1043A

2884P/1045A

- 72 -

171411A

mmoles) and allyl bromide (6.0 gm; 50 mmoles) in acetone (100 mL) was refluxed for a period of 18 hours. The reaction mixture was cooled, filtered through Celite (diatomaceous earth) and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 11.2 gm (97%) of 2-hydroxy-5-allyloxyacetophenone, mp. 51-53°C.

¹H NMR 2.60 (s, 3H, CH₃), 4.52 (d, J=6 Hz, 2H, OCH₂), 5.30 (m, 1H, CH), 6.00 (m, 2H, CH₂), 6.83 (d, J=9Hz, 1H, proton ortho to hydroxyl), 7.13 (m, 2H, proton ortho to allyloxy).

Anal. Calcd for C₁₁H₁₂O₃: C, 68.75; H, 6.25.
Found: C, 68.74; H, 6.53.

b) Preparation of 2-(p-fluorobenzoyl)-3-methyl-5-allyloxybenzofuran

20

A mixture of 2-hydroxy-5-allyloxyacetophenone (5.0 gm; 26 mmoles), potassium carbonate (3.9 gm; 28 mmoles) and p-fluorophenacylbromide (6.2 gm; 28 mmoles) in methylethylketone (75 mL) was refluxed for a period of 22 hours. The reaction mixture was cooled, filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethylacetate in hexane as eluent to yield 3.9 gm (48%) of 2-(p-fluorobenzoyl)-3-methyl-5-allyloxybenzofuran, mp. 80-82°C.

30

¹H NMR 2.67 (s, 3H, CH₃), 4.60 (m, 2H, CH₂), 5.43 (m, 2H, CH₂), 6.13 (m, 1H, CH), 7.20 (d, 3H, J

2882P/1043A

2884P/1045A

- 73 -

171411A

= 9 Hz, protons ortho to fluoro and H7), 7.27 (d, J=3 Hz, 1H, H4), 7.47 (d of d, J= 3 Hz, 9 Hz, H6), 8.18 (d of d, 2H, J= 5 Hz, 9 Hz, protons ortho to carbonyl).

5

Anal. Calcd for $C_{19}H_{15}FO_3$: C, 73.53; H, 4.87; F, 6.12. Found: C, 73.98; H, 4.85; F, 6.08.

10 c) Preparation of 2-(p-fluorobenzoyl)-3-methyl-4-allyl-5-hydroxybenzofuran

A solution of 2-(p-fluorobenzoyl)-3-methyl-5-allyloxybenzofuran (2.77 gm; 9.2 mmoles) in ortho-dichlorobenzene (15 mL) was refluxed under nitrogen for a period of 4 hours. On cooling, the reaction product crystallized. Some hexane was added and the crystals were filtered, washed with hexane and air-dried to yield 2.1 gm (76%) of 2-(p-fluorobenzoyl)-3-methyl-4-allyl-5-hydroxybenzofuran, mp. 164-166°C.

¹H NMR 2.80 (s, 3H, CH₃), 3.80 (m, 2H, CH₂), 5.07 (m, 2H, CH₂), 7.20 (m, 4H, protons ortho to fluoro, H5 and H7), 8.10 (d of d, 2H, J= 5 Hz, 9 Hz, protons ortho to carbonyl).

Anal. Calcd for $C_{19}H_{15}FO_3$: C, 73.53; H, 4.87; F, 6.12. Found: C, 73.53; H, 4.84; F, 6.33.

30 d) Preparation of 2-(p-fluorobenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran

2882P/1043A

2884P/1045A

- 74 -

171411A

A solution of 2-(p-fluorobenzoyl)-3-methyl-4-allyl-5-hydroxybenzofuran (1.5 gm; 4.8 mmoles) in ethanol (50 mL) was hydrogenated in a Parr apparatus in presence of 10% palladium on carbon. The catalyst
5 was removed by filtration and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 600 mg (42%) of
2-(p-fluorobenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran, mp 121-123°C.
10

^1H NMR 0.97 (t, 3H, J = 7 Hz, CH_3), 1.63 (sextet, 2H, J = 7 Hz, CH_2), 2.27 (s, 3H, CH_3), 2.83 (t, 2H, J = 7 Hz, CH_2), 3.93 (s, 2H, CH_2), 4.40 (s, 15 2H, CH_2), 6.90 (m, 6H, aromatic protons).

Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{FO}_2$: C, 76.48; H, 6.41; F, 6.36. Found: C, 76.11; H, 6.48; F, 6.55.

20

EXAMPLE 112-(4-hydroxybenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran

25 Under nitrogen, ethanethiol (3.1 gm; 50 mmoles) was added dropwise over 5 minutes to a mixture of 99% sodium hydride (1.2 gm; 50 mmoles) in dimethylformamide (100 mL). After stirring for 15 minutes, a solution of 2-(4-methoxybenzyl)-3-methyl-
30 4-propyl-5-hydroxybenzofuran (2.1 gm; 6.7 mmoles) in dimethylformamide (DMF) (25 mL) was added in one portion. The mixture was refluxed for 1.5 hours, cooled, acidified with 20% citric acid and extracted

2882P/1043A

2884P/1045A

- 75 -

171411A

with ether. The ether solution was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil crystallised on standing at room temperature overnight. The crystals were
5 slurried with hexane, filtered, washed with hexane, and air-dried to yield 2-(4-hydroxybenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran, mp. 138-142°C.

^1H NMR 1.03 (t, 3H, J = 7 Hz, CH_3), 1.67 (sextet, 2H, J = 7 Hz, CH_2), 2.37 (s, 3H, CH_3), 2.90 (t, 2H, J = 7 Hz, CH_2), 3.80 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.50 (s, 2H, CH_2), 6.53 (d, 1H, J = 9Hz, H6), 6.80 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.07 (d, 1H, J = 9Hz, H7) 7.20 (d, 2H, J =
15 9Hz, protons meta to methoxy).

Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_3$: C, 77.00; H, 6.80.
Found: C, 77.64; H, 6.66.

20

EXAMPLE 12

2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-chloro-7-propylbenzofuran

25 a) Preparation of 2-hydroxy-3-chloro-6-allyloxy-acetophenone

A mixture of 2,6-dihydroxy-3-chloroacetophenone (1.2 gm; 6.2 mmoles), potassium carbonate (855 mg; 6.2 mmoles) and allyl bromide (562 μl ; 6.5 mmoles) in acetone (30 mL) was refluxed for a period of two hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo.

2882P/1043A

2884P/1045A

- 76 -

171411A

The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 627 mg (45%) of 2-hydroxy-3-chloro-6-allyloxyacetophenone.

- 5 ^1H NMR 2.74 (s, 3H, CH_3), 4.55 (d, $J=6$ Hz, 2H, OCH_2), 5.40 (m, 2H, CH_2), 6.10 (m, 1H, CH), 6.76 (d, $J=9$ Hz, 1H, H5), 7.43 (d, $J=9$ Hz, 1H, H4).

- 10 b) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-allyloxy-5-chlorobenzofuran

- 15 A mixture of 2-allyloxy-3-chloro-6-hydroxyacetophenone (587 mg; 2.6 mmoles), potassium carbonate (357 mg; 2.6 mmoles) and p-methoxyphenacyl bromide (590 mg; 2.6 mmoles) in acetone (15 mL) was refluxed for a period of 18 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield
- 20 2-(p-methoxybenzoyl)-3-methyl-4-allyloxy-5-chlorobenzofuran.

- 25 ^1H NMR 2.73 (s 3H, CH_3), 3.88 (s, 3H, CH_3), 4.62 (d, 2H, $J=6$ Hz, CH_2), 5.40 (m, 2H, CH_2), 6.16 (m, 1H, CH_2), 7.00 (d, 2H, $J=9$ Hz, protons ortho to methoxy), 7.23 (d, $J=9$ Hz, 1H, H6), 7.41 (d, $J=9$ Hz, 1H, H5), 8.08 (d, 2H, $J=9$ Hz, protons ortho to carbonyl).

- 30 c) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-chloro-7-allyl-benzofuran

2882P/1043A

2884P/1045A

- 77 -

171411A

A mixture of 2-(p-methoxybenzoyl)-3-methyl-4-allyloxy-5-chlorobenzofuran (400 mg; 1.12 mmoles) in ortho-dichlorobenzene (15 mL) was refluxed under nitrogen for 1.5 hours. The reaction mixture was cooled to room temperature and purified by chromatography on silica gel using 20% ethylacetate as eluent to yield 110 mg (27%) of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-chloro-7-allylbenzofuran.

¹H NMR 2.79 (s, 3H, CH₃), 3.54 (d, 2H, J = 6Hz, CH₂), 3.90 (s, 3H, CH₃), 5.15 (m, 2H, CH₂), 5.96 (m, 1H, CH₂), 6.96 (d, 2H, J = 9Hz, protons ortho to methoxy), 7.17 (s, 1H, H₆), 8.12 (d, 2H, J = 9 Hz, protons ortho to carbonyl).

15

d) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-chloro-7-propylbenzofuran

A solution of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-chloro-7-allylbenzofuran (110 mg; 0.31 mmole) in ethanol (15 mL) was hydrogenated in a Parr apparatus at 20 psi in the presence of 5% palladium on charcoal. The catalyst was filtered off and the filtrate was evaporated in vacuo to yield 110 mg of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-chloro-7-propylbenzofuran.

¹H NMR 0.93 (t, J= 7 Hz, 3H, CH₃), 1.70 (sextet, J=7 Hz, 2H, CH₂), 2.38 (s, 3H, CH₃), 2.76 (t, J=7Hz, 2H, CH₂), 2.79 (s, 3H, CH₃), 3.90 (s, 3H, CH₃), 5.80 (s, 1H, OH), 7.00 (d, J=9 Hz, 2H, protons ortho to methoxy), 7.15 (s, 1H, H₆), 8.10 (d, J=9 Hz, 2H, proton meta to methoxy).

30

2882P/1043A

2884P/1045A

- 78 -

171411A

e) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-chloro-7-propylbenzofuran

A solution of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-chloro-7-propylbenzofuran (90 mg; 0.25 mmole), hydrazine (80 μ l) and potassium hydroxide (98 mg) in ethylene glycol (2 mL) was heated at 145°C for a period of 5 hours. The reaction mixture was cooled, poured in water, and extracted with ether. The organic phase was washed with 20% citric acid, with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 47 mg (50%) of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-chloro-7-propylbenzofuran.

^1H NMR 0.93 (t, J= 7 Hz, 3H, CH_3), 1.66 (sextet, J=7 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.70 (t, J=7Hz, 2H, CH_2), 3.78 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 5.50 (s, 1H, OH), 6.84 (d, J=9 Hz, 2H, protons ortho to methoxy), 6.91 (s, 2H, H6), 7.15 (d, J=9 Hz, 2H, proton meta to methoxy).

EXAMPLE 13

25

2-(p-methoxybenzyl)-3-methyl-6-hydroxy-7-propylbenzofuran

30

a) Preparation of 4-benzyloxy-3-propyl-2-hydroxyacetophenone

A mixture of 2,4-dihydroxy-3-propyl-acetophenone (5.8 gm; 30 mmoles), potassium carbonate (8.3

2882P/1043A

2884P/1045A

- 79 -

171411A

- gm; 60 mmoles) and benzylbromide (5.6 gm; 33 mmoles) in methylethylketone (60 mL) was refluxed for a period of 4 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo.
- 5 The residue crystallized on stirring with hexane. It was filtered, washed with hexane, and air-dried to yield 6.67 gm (78%) 4-benzyloxy-3-propyl-2-hydroxy-acetophenone.

10 b) Preparation of 2-(p-methoxybenzoyl)-3-methyl-6-benzyloxy-7-propylbenzofuran

- Sodium hydride (0.66 gm; 27.5 mmoles) was added to an ice-cold mixture of 4-benzyloxy-3-propyl-2-hydroxyacetophenone (6.4 gm, 22.5 mmoles) and dimethylformamide (64 mL). After stirring for 30 minutes, more sodium hydride (0.4 gm, 17.5 mmoles) was added, followed by p-methoxyphenacyl bromide (2.91 gm, 12.7 mmoles). The reaction was stirred for
- 20 24 hours at room temperature. The mixture was poured on ice and a slight excess of hydrochloric acid was added. The resulting mixture was extracted with ether. The organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated in
- 25 vacuo. The residue crystallized from methanol. The solid was filtered, washed with methanol, and air-dried to yield 2- (p-methoxybenzoyl)-3-methyl-6-benzyloxy-7-propylbenzofuran, mp. 105-106°C.

30 c) Preparation of 2-(p-methoxybenzyl)-3-methyl-6-benzyloxy-7-propylbenzofuran

A solution of 2-(p-methoxybenzoyl)-3-methyl-6-benzyloxy-7-propylbenzofuran (1.04 gm, 2.5

2882P/1043A

2884P/1045A

- 80 -

171411A

mmoles) in ethanol (100 mL) was hydrogenated in a Parr hydrogenator in the presence of 10% palladium on charcoal for a period of 24 hours. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel and eluted with 25% ethylacetate in hexane to yield 110 mg of 2-(p-methoxybenzyl)-3-methyl-6-hydroxy-7-propylbenzofuran.

¹H NMR 0.97 (t, 3H, J = 9 Hz, CH₃), 1.63 (sextet, 2H, J = 7 Hz, CH₂), 2.17 (s, 3H, CH₃), 2.80 (t, 2H, J = 7 Hz, CH₂), 3.80 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 4.63 (s, 1H, OH), 6.70 (d, 1H, J = 9 Hz, H5), 6.83 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.13 (d, 1H, J = 9 Hz, H4), 7.17 (d, 2H, J = 9 Hz, protons meta to methoxy)

EXAMPLE 14

20

2-(p-methoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-fluorobenzofuran

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (0.10 gm, 0.3 mmoles), acetic anhydride (0.5 mL) and triethylamine (0.7 mL) in tetrahydrofuran (15 mL) was stirred at room temperature overnight. The volatiles were removed in vacuo and the residue was purified by chromatography on silica gel and eluted with 15% ethylacetate in hexane to yield 90 mg (80%) of 2-(p-methoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-fluorobenzofuran, mp. 85-88°C.

2882P/1043A

2884P/1045A

- 81 -

171411A

¹H NMR 0.97 (t, 3H, J = 9 Hz, CH₃), 1.53 (sextet, 2H, J = 7 Hz, CH₂), 2.17 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.53 (t, 2H, J = 7 Hz, CH₂), 3.77 (s, 3H, CH₃), 3.98 (s, 2H, CH₂), 6.73 (m, 3H, H6 and protons ortho to methoxy), 7.13 (d, 2H, J = 9 Hz, protons meta to methoxy).

EXAMPLE 15

10 2-(p-methoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-
chlorobenzofuran

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (0.10 gm, 0.29 mmoles), acetic anhydride (0.5 mL) and triethylamine (1.0 mL) in tetrahydrofuran (15 mL) was stirred at room temperature overnight. The volatiles were removed in vacuo. The residue was purified by chromatography on silica gel and eluted with 15% ethylacetate in hexane to yield 100 mg (91%) of 2-(p-methoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran, mp. 119-120°C.

25 ¹H NMR 0.97 (t, 3H, J = 9 Hz, CH₃), 1.53 (sextet, 2H, J = 7 Hz, CH₂), 2.20 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.53 (t, 2H, J = 7 Hz, CH₂), 3.80 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 6.80 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.07 (s, 1H, H6), 7.10 (d, 2H, J = 9 Hz, protons meta to methoxy).

30

2882P/1043A

2884P/1045A

- 82 -

171411A

EXAMPLE 162-(p-methoxybenzyl)-3-methyl-4-propyl-5-acetoxy-benzofuran

5

A solution of 2-(p-methoxybenzyl)-3-methyl-4-propyl-5-hydroxy-benzofuran (1.2 gm, 3.87 mmoles), acetic anhydride (0.5 mL) and triethylamine (1.0 mL) in tetrahydrofuran (15 mL) was stirred at room temperature overnight. The volatiles were removed in vacuo. The residue was purified by chromatography on silica gel and eluted with 15% ethylacetate in hexane to yield 1.2 gm (79%) of 2-(p-methoxybenzyl)-3-methyl-4-propyl-5-acetoxybenzofuran, mp. 39-41°C.

15

^1H NMR 1.00 (t, 3H, $J = 9$ Hz, CH_3), 1.57 (sextet, 2H, $J = 7$ Hz, CH_2), 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.78 (t, 2H, $J = 7$ Hz, CH_2), 3.73 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.80 (d, 1H, $J = 9$ Hz, H6), 6.83 (d, 2H, $J = 9$ Hz, protons ortho to methoxy), 7.10 (d, 2H, $J = 9$ Hz, protons meta to methoxy), 7.17 (d, 1H, $J = 9$ Hz, H7).

20

EXAMPLE 17

25

2-(p-methoxybenzyl)-3-methyl-4-ethoxycarbonyloxy-5-propyl-7-fluorobenzofuran

30

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (0.10 gm, 0.3 mmoles), ethyl chloroformate (0.1 mL) and triethylamine (0.7 mL) in tetrahydrofuran (15 mL) was stirred at room temperature overnight. The volatiles were

2882P/1043A

2884P/1045A

- 83 -

171411A

removed in vacuo. The residue was purified by chromatography on silica gel and eluted with 15% ethylacetate in hexane to yield 90 mg (80%) of 2-(p-methoxybenzyl)-3-methyl-4-ethoxycarbonyloxy-5-propyl-7-fluorobenzofuran, mp. 85-88°C.

¹H NMR 0.97 (t, 3H, J = 9 Hz, CH₃), 1.53 (sextet, 2H, J = 7 Hz, CH₂), 2.17 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.53 (t, 2H, J = 7 Hz, CH₂), 3.77 (s, 3H, CH₃), 3.98 (s, 2H, CH₂), 6.73 (m, 3H, H6 and protons ortho to methoxy), 7.13 (d, 2H, J = 9 Hz, protons meta to methoxy).

EXAMPLE 18

15

2-(p-methoxybenzyl)-3-methyl-4-ethoxycarbonyloxy-5-propyl-7-chlorobenzofuran

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (0.10 gm, 0.29 mmoles), ethyl chloroformate (0.1 mL) and triethylamine (1.0 mL) in tetrahydrofuran (15 mL) was stirred at room temperature overnight. The volatiles were removed in vacuo. The residue was purified by chromatography on silica gel and eluted with 15% ethylacetate in hexane to yield 100 mg (91%) of 2-(p-methoxybenzyl)-3-methyl-4-ethoxycarbonyloxy-5-propyl-7-chlorobenzofuran, mp. 99-100°C.

¹H NMR 0.97 (t, 3H, J = 9 Hz, CH₃), 1.53 (sextet, 2H, J = 7 Hz, CH₂), 2.20 (s, 3H, CH₃), 2.53 (t, 2H, J = 7 Hz, CH₂), 3.78 (s, 3H, CH₃), 3.98 (s, 3H, CH₃), 4.07 (s, 2H, CH₂), 6.87 (d, 2H, J = 9

2882P/1043A

2884P/1045A

- 84 -

171411A

Hz, protons ortho to methoxy), 7.17 (s, 1H, H₆), 7.20 (d, 2H, J = 9 Hz, protons meta to methoxy).

EXAMPLE 19

5

2-(p-methoxybenzyl)-3-methyl-4-propyl-5-ethoxycarbonyloxy-benzofuran

10 A solution of 2-(p-methoxybenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran (1.2 gm, 3.87 mmoles), ethyl chloroformate (0.1 mL) and triethylamine (1.0 mL) in tetrahydrofuran (15 mL) was stirred at room temperature overnight. The volatiles were removed in vacuo. The residue was purified by chromatography on
15 silica gel and eluted with 15% ethylacetate in hexane to yield 1.2 gm (79%) of 2-(p-methoxybenzyl)-3-methyl-4-propyl-5-ethoxycarbonyloxybenzofuran, mp. 51-53°C.

20 ¹H NMR 1.00 (t, 3H, J = 9 Hz, CH₃), 1.60 (sextet, 2H, J = 7 Hz, CH₂), 2.33 (s, 3H, CH₃), 2.83 (t, 2H, J = 7 Hz, CH₂), 3.80 (s, 3H, CH₃), 3.93 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 6.80 (d, 1H, J = 9 Hz, H₆), 6.90 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.18 (d, 2H, J = 9 Hz, protons meta to
25 methoxy), 7.23 (d, 1H, J = 9 Hz, H₇).

EXAMPLE 20

30 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-bromobenzofuran

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-benzofuran (1 gm; 3.22 mmoles) in

2882P/1043A

2884P/1045A

- 85 -

171411A

methylen chloride (30 mL) was cooled at 0°C and
bromine (0.52 gm; 3.22 mmoles) in methylen chloride
(10 mL) was added dropwise. The reaction mixture was
stirred for 15 minutes. The reaction mixture was
5 washed with a saturated sodium bicarbonate solution,
dried (Na_2SO_4), and concentrated in vacuo. The
residue was purified by preparative TLC, eluting with
15% ethylacetate in hexane to yield 2-(p-methoxy-
benzyl)-3-methyl-4-hydroxy-5-propyl-7-bromo
10 benzofuran, mp. 110-112°C.

^1H NMR 0.98 (t, $J=7$ Hz, 3H, CH_3), 1.63 (sextet,
 $J=7$ Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.55 (t,
 $J=7$ Hz, 2H, CH_2), 3.78 (s, 6H, CH_3), 4.00 (s, 2H,
15 CH_2), 4.97 (s, 1H, OH), 6.83 (d, $J=9$ Hz, 2H,
protons ortho to methoxy), 7.07 (s, 1H, H6), 7.17 (d,
 $J=9$ Hz, 2H, proton meta to methoxy).

EXAMPLE 21

20

2-(p-methoxybenzyl)-3,7-dimethyl-4-hydroxy-5-propyl
benzofuran

a) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-
25 hydroxy-5-propyl-7-dimethylaminomethylbenzofuran

A solution of 2-(p-methoxybenzyl)-3-methyl-
4-hydroxy-5-propyl-benzofuran (155 mg gm; 0.5 mmole)
in methylen chloride (2 mL) was reacted with
30 Eschenmoser's salt (dimethyl-methylene ammonium
iodide) (105 mg; 0.5 mmole) overnight at room
temperature. The reaction mixture was concentrated
in vacuo. The residue was taken up in ethylacetate.

2882P/1043A

2884P/1045A

- 86 -

171411A

potassium carbonate was added and the mixture was stirred for a period of 15 minutes. The solids were separated and the ethylacetate solution was evaporated to yield 228 mg of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-dimethylaminomethylbenzofuran.

¹H NMR 0.98 (t, J= 7 Hz, 3H, CH₃), 1.70 (sextet, J=7 Hz, 2H, CH₂), 2.33 (s, 6H, CH₃N), 2.43 (s, 3H, CH₃), 2.63 (t, J=7Hz, 2H, CH₂), 3.73 (s, 2H, CH₂N), 3.83 (s, 3H, CH₃O), 4.07 (s, 2H, CH₂), 4.90 (s, 1H, OH), 6.90 (d, J=9 Hz, 2H, protons ortho to methoxy), 6.93 (s, 1H, H6), 7.23 (d, J=9 Hz, 2H, proton meta to methoxy).

15

b) Preparation of 2-(p-methoxybenzyl)-3,7-dimethyl-4-hydroxy-5-propylbenzofuran

To a solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-dimethylaminomethylbenzofuran (0.2 gm; 0.54 mmole) in ethanol (5 mL) was added sodium borohydride (0.2 gm, 5.45 mmoles) and the reaction mixture was refluxed for 10 minutes. The reaction mixture was cooled, poured in a saturated solution of ammonium chloride, and extracted with ether. The organic phase was washed with with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 160 mg (91%) of 2-(p-methoxybenzyl)-3,7-dimethyl-4-hydroxy-5-propylbenzofuran, mp. 102-104°C.

2882P/1043A

2884P/1045A

- 87 -

171411A

¹H NMR 0.98 (t, J= 7 Hz, 3H, CH₃), 1.67 (sextet, J=7 Hz, 2H, CH₂), 2.37 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 2.63 (t, J=7Hz, 2H, CH₂), 3.78 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 4.60 (s, 1H, OH), 6.73 (s, 1H, H₆), 6.83 (d, J=9 Hz, 2H, protons ortho to methoxy), 7.20 (d, J=9 Hz, 2H, proton meta to methoxy).

Anal. Calcd for C₂₁H₂₄O₃: C, 77.73; H, 7.46;
10 Found: C, 77.88; H, 7.55.

EXAMPLE 22

15 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5,7-dipropyl benzofuran

a) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5,7-dipropylbenzofuran

20 A mixture of 2,6-dihydroxy-3,5-dipropylaceto-
phenone (3.38 gm; 14.3 mmoles), potassium carbonate
(1.97 gm; 14.3 mmoles) and p-methoxy-phenacylbromide
(3.27 gm; 14.3 mmoles) in acetone (50 mL) was
25 refluxed for a period of eighteen hours. The
reaction mixture was cooled, filtered through Celite,
and concentrated in vacuo. The residue was
chromatographed on silica gel using 20% ethylacetate
in hexane as eluent to yield 0.40 gm (8%) of
30 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5,7-dipropyl-
benzofuran, mp. 119-121°C.

¹H NMR 0.93 (t, J= 7 Hz, 3H, CH₃), 0.98 (t, J= 7
Hz, 3H, CH₃), 1.66 (sextet, J=7 Hz, 4H, CH₂).

2882P/1043A

2884P/1045A

- 88 -

171411A

2.60 (t, J=7Hz, 2H, CH₂), 2.70 (t, J=7Hz, 2H, CH₂), 2.80 (s, 3H, CH₃), 3.90 (s, 3H, CH₃), 5.00 (s, 1H, OH), 6.93 (s, 1H, H6), 6.98 (d, J=9 Hz, 2H, proton ortho to methoxy), 8.13 (d, J= 9Hz, 2H, proton ortho to carbonyl).

5

b) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5,7-dipropylbenzofuran

10

A mixture of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5,7-dipropylbenzofuran (0.30 gm; 0.80 mmoles), 99% hydrazine (0.2 mL), potassium hydroxide (0.40 gm; 7 mmoles) in ethylene glycol (10 mL) was heated at 140°C for a period of 2.5 hours and at 195°C for one hour. The reaction mixture was cooled, poured into water, and extracted with ethylacetate. The organic phase was washed with 20% citric acid, with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 140 mg (50%) of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5,7-dipropylbenzofuran, mp. 70-72°C.

15

20

¹H NMR 0.93 (t, J= 7 Hz, 3H, CH₃), 0.98 (t, J= 7 Hz, 3H, CH₃), 1.63 (sextet, J=7 Hz, 2H, CH₂), 1.68 (sextet, J=7 Hz, 2H, CH₂), 2.38 (s, 3H, CH₃), 2.60 (t, J= 7 Hz, 2H, CH₂), 2.68 (t, J= 7 Hz, 2H, CH₂), 3.77 (s, 3H, CH₃), 3.93 (s, 2H, CH₂), 4.70 (s, 1H, OH), 6.70 (s, 2H, H6 and H7), 6.80 (d, J=9 Hz, 2H, proton ortho to methoxy), 6.90 (s, 1H, H6), 7.17 (d, J= 9Hz, 2H, proton meta to methoxy).

25

30

2882P/1043A

2884P/1045A

- 89 -

171411A

Anal. Calcd for $C_{20}H_{22}O_3$: C, 78.37; H, 8.00;

Found: C, 77.82; H, 7.70.

EXAMPLE 23

.5

2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

- 10 a) Preparation of 2,6-dihydroxy-3-propyl-5-chloroacetophenone

15 A mixture of 2,6-dihydroxy-3-propylacetophenone (40 gm, 0.206 mole) and N-chlorosuccinimide (40 gm; 0.300 mole) in methylene chloride (3 liters) was stirred at room temperature for a period of two days. The reaction mixture was poured onto a 3 liter fritted-disk funnel filled with silica gel and elution was carried out with methylene chloride. Evaporation of the filtrate yielded 2,6-dihydroxy-3-propyl-5-chloroacetophenone; m.p.: 64-65°C.

25 1H NMR 0.93 (t, J= 7 Hz, 3H, CH_3), 1.63 (sextet, J=7 Hz, 2H, CH_2), 2.53 (t, J=7Hz, 2H, CH_2), 2.73 (s, 3H, CH_3), 6.33 (s, 1H, proton ortho to chloro), 13.13 (s, 1H, OH).

- b) Preparation of 2-carboethoxymethoxy-6-hydroxy-3-chloro-5-propylacetophenone

30 A mixture of 2,6-dihydroxy-5-chloro-3-propylacetophenone (38.5 gm, 0.169 mole), ethyl bromoacetate (18.6 ml; 0.169 mole) and potassium carbonate (23.24 gm; 0.169 mole) in acetone (3 liters)

2882P/1043A

2884P/1045A

- 90 -

171411A

- was refluxed for a period of 2.5 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel and eluted with 5% ethyl acetate in hexane to yield 2-carboethoxymethoxy-6-hydroxy-3-chloro-5-propylacetophenone.

^1H NMR 0.93 (t, J = 7 Hz, 3H, CH_3), 1.30 (t, J = 7 Hz, 3H, CH_3), 1.63 (sextet, J = 7 Hz, 2H, CH_2), 2.57 (t, J = 7 Hz, 2H, CH_2), 2.77 (s, 3H, CH_3), 4.27 (q, J = 7 Hz, 2H, CH_2O), 4.73 (s, 2H, CH_2), 7.23 (s, 1H, proton ortho to chloro), 12.50 (s, 1H, OH).

- c) Preparation of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran.

To a solution of 2-carboethoxymethoxy-6-hydroxy-3-chloro-5-propylacetophenone (43 gm; 0.136 mole) in freshly-distilled absolute ethanol (1.2 liter) was brought to reflux and a 1M solution of sodium ethoxide (273 mL; 0.273 mole) was added rapidly. The reaction mixture was refluxed for a period of 1 hour. It was cooled to room temperature and poured into 0.5N hydrochloric acid and extracted with ethylacetate. The organic phase was dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 15% ethylacetate in hexane to yield 22.0 gm of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran; m.p.: 165-166°.

2882P/1043A

2884P/1045A

- 91 -

171411A

¹H NMR 1.00 (t, J= 7 Hz, 3H, CH₃), 1.25 (t, J=7 Hz, 3H, CH₃), 1.63 (sextet, J=7 Hz, 2H, CH₂), 2.57 (t, J=7Hz, 2H, CH₂), 2.76 (s, 3H, CH₃), CH₂), 4.43 (q, J=7 Hz, 2H, CH₂O), 5.19 (s, 1H, OH), 7.15 (s, 1H, proton ortho to chloro), 5.19 (s, 1H, OH).

3-methyl-4-hydroxy-5-propyl-7-chlorobenzo-furan was also obtained; m.p.: 49-50°C.

10

¹H NMR 0.97 (t, J= 7 Hz, 3H, CH₃), 1.60 (sextet, J=7 Hz, 2H, CH₂), 2.32 (s, 3H, CH₃), CH₂), 2.50 (t, J=7Hz, 2H, CH₂), 4.97 (s, 1H, OH), 6.93 (s, 1H, proton ortho to chloro), 7.20 (s, 1H, H₂).

15

Anal. Calcd for C₁₂H₁₃ClO₂: C, 64.58; H, 6.20; Cl, 15.72. Found: C, 64.14; H, 5.79; Cl, 15.81.

d) Preparation of 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran carboxylic acid

20

To a solution of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (22 gm, 0.074 mole) in methanol (1.2 liter) was added 2N sodium hydroxide (120 mL) and the resulting solution was refluxed for a period of 6 hours. The reaction mixture was concentrated in vacuo. The residue was acidified with 3N hydrochloric acid and then extracted with ethylacetate. The organic phase was dried (Na₂SO₄), concentrated in vacuo, and 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofurancarboxylic acid (17 gm, 88%) was isolated by filtering the solid after suspending in hexane; m.p.: 200-203°C.

30

2882P/1043A

2884P/1045A

- 92 -

17141IA

^1H NMR 0.97 (t, $J = 7$ Hz, 3H, CH_3), 1.60 (sextet, $J = 7$ Hz, 2H, CH_2), 2.60 (t, $J = 7$ Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 7.33 (s, 1H, proton ortho to chloro), 7.60 (s, 1H, OH).

5

e) Preparation of 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

A mixture of 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran carboxylic acid (0.93 gm; 3.7 mmoles), toluene (25 mL), 6N hydrochloric acid (20 mL), 10N HCl (100 mL) and acetic acid (30 mL) was refluxed for a period of 18 hours. The two phases were separated and the organic phase was dried (Na₂SO₄), and concentrated in vacuo to yield 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (0.62 gm; 80%), identical to the product obtained from the cyclisation reaction described above in Step C.

20 f) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-(p-methoxybenzoyloxy)-5-propyl-7-chlorobenzofuran

A solution of p-anisoyl chloride (3.5 gm; 20.5 mmoles) in ethylene dichloride (10 mL) was added slowly to a cooled suspension of aluminium chloride (4.0 gm; 30 mmoles) in ethylene dichloride (100 mL). After stirring for a period of 10 minutes, 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (1.14 gm; 5 mmoles) in dichloroethylene (5 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 1 hour. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic

2882P/1043A

2884P/1045A

- 93 -

171411A

layer was separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was

5 chromatographed on silica gel and eluted with 10% ethylacetate in hexane to yield 1.92 gm (78%) of 2-(p-methoxybenzoyl)-3-methyl-4-(p-methoxybenzoyloxy)-5-propyl-7-chlorobenzofuran, mp. 103-105°C.

10 ^1H NMR 0.97 (t, $J = 7$ Hz, 3H, CH_3), 1.63 (sextet, $J = 7$ Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.63 (t, $J = 7$ Hz, 2H, CH_2), 3.93 (s, 6H, CH_3), 7.07 (d, $J = 9$ Hz, 1H, proton ortho to methoxy), 7.13 (d, $J = 9$ Hz, 1H, proton ortho to methoxy), 8.23 (d, $J = 9$ Hz, 1H, proton ortho to methoxy), 7.27 (d, $J = 9$ Hz, 1H, proton ortho to methoxy).

Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{ClO}_3$: C, 69.66; H, 6.13; Cl, 10.28.
Found: C, 69.80; H, 6.18; Cl, 10.23.

20

g) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

To an ice-cold suspension of aluminium chloride (467 mg, 3.5 mmoles) in ether (100 mL) was added slowly lithium aluminium hydride (570 mg, 15 mmoles). After stirring for a period of 10 minutes, 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (491 mg, 1 mmole) in ether (10 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 10 minutes. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided,

2882P/1043A

2884P/1045A

- 94 -

171411A

the organic layer was separated and the aqueous phase was extracted with ether. The organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromato-

- 5 graphed on silica gel and eluted with 10% ethyl acetate in hexane to yield 0.30 gm (87%) of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, mp. 103-105 C.

- 10 ^1H NMR 1.00 (t, $J=7$ Hz, 3H, CH_3), 1.64 (sextet, $J=7$ Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.57 (t, $J=7$ Hz, 2H, CH_2), 3.79 (s, 6H, CH_3), 4.03 (s, 2H, CH_2), 6.84 (d, $J=9$ Hz, 1H, proton ortho to methoxy), 6.93 (s, 1H, proton ortho to chloro), 7.18
- 15 (d, $J=9$ Hz, 1H, proton meta to methoxy).

Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{ClO}_3$: C, 69.66; H, 6.13; Cl, 10.28.
Found: C, 69.80%; H, 6.18; Cl, 10.23.

- 20 Following the procedure of Example 23, step (e), the compounds of Table 23-1 were prepared from the appropriate precursor acids described in U.S. Ser. No. 661,645, filed October 17, 1984 (Attorney Docket No. 169601A).

25

30

2882P/1043A

0165810

2884P/1045A

- 95 -

171411A

TABLE 23-1

	<u>R1</u>	<u>R2</u>	<u>R3</u>	<u>X</u>	<u>Y</u>	<u>Y1</u>	<u>M.P. (°C)</u>
5	Me	H	5,6-OCH ₂ O	O	H	H	48-50
	Me	H	4-OMe	O	7-Pr	H	OIL
	Me	H	7-OH	O	H	H	90-91
	Me	H	4-OH	O	7-Pr	H	65-66
	Me	H	5-OH	O	H	H	84-5
10	Me	H	4-OH	O	5-allyl	H	OIL
	Pr	H	4-OH	O	H	H	35-36
	Pr	H	4-allyl	O	H	H	OIL
	Pr	H	4-OH	O	5-allyl	H	OIL
	Me	H	5-Oallyl	O	H	H	OIL
15	Me	H	5-OH	O	4-allyl	H	65-67
	Me	H	5-OH	O	4-Pr	H	83-85
	Me	H	4-OH	O	5-Pr	H	35-36
	C ₆ H ₅	H	4-OH	O	H	H	OIL
	Me	H	4-OH	O	H	H	110-112
20							
25							
30							

2882P/1043A

2884P/1045A

- 96 -

171411A

EXAMPLE 242-(p-methoxybenzyl)-3-methyl-5-hydroxybenzofuran

- 5 a) Preparation of 2-(p-methoxybenzoyl)-3-methyl-5-(p-methoxyphenacyloxy)-benzofuran

A mixture of 2,5-dihydroxyacetophenone (2.78 gm; 18.3 mmoles), potassium carbonate (5.06 gm; 36.6
10 mmoles) and p-methoxyphenacyl bromide (8.4 gm, 36.8 mmoles) in acetone (100 mL) was refluxed for a period of 18 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo.
The residue was taken up in a minimum volume of
15 acetone and the solution was left to crystallize. The crystals were filtered, washed with cold ethylacetate, and air-dried to yield 4.0 gm (51%) of 2-(p-methoxybenzoyl)-3-methyl-5-(p-methoxyphenacyloxy)-benzofuran, mp. 155-157°C.

20

^1H NMR 2.60 (s, 3H, CH_3), 3.93 (s, 6H, CH_3),
5.30 (s, 2H, CH_2), 7.00 (m, 4H, protons ortho to methoxyl), 7.20 (m, 2H, H6 and H7), 8.10 (t, 2H, J = 9 Hz, protons meta to methoxy).

25

Anal: Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 72.54; H, 5.15.
Found: C, 72.57; H, 5.22.

- 30 b) Preparation of 2-(p-methoxybenzyl)-3-methyl-5-hydroxybenzofuran

2882P/1043A

2884P/1045A

- 97 -

171411A

A mixture of 2-(p-methoxybenzoyl)-3-methyl-5-(p-methoxyphenacyloxy)-benzofuran (5.35 gm, 12.4 mmoles) and zinc dust (5.3 gm) in acetic acid (200 mL) was stirred at room temperature overnight. The solids were filtered off and washed with some ethylacetate. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 0.85 gm (26%) of 2-(p-methoxybenzyl)-3-methyl-5-hydroxybenzofuran, mp. 128-131°C.

^1H NMR 2.17 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 6.90 (m, 7H, aromatic protons)

Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3$: C, 76.09; H, 6.01.
Found: C, 76.35; H, 6.37.

EXAMPLE 25

2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran

a) Preparation of 2-hydroxy-6-allyloxyacetophenone

A mixture of 2,6-dihydroxyacetophenone (300 gm; 1.97 moles), potassium carbonate (271 gm; 1.97 moles), and allyl bromide (271 mLs; 2.25 moles) in acetone (10 liters) was refluxed for a period of 3 hours. The reaction mixture was cooled, filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel using toluene as eluent to yield 305 gm (80%) of 2-hydroxy-6-allyloxyacetophenone, mp. 54-55°C.

2882P/1043A

2884P/1045A

- 98 -

171411A

- ^1H NMR 2.40 (s, 3H, CH_3), 4.57 (d, $J=6$ Hz, 2H, OCH_2), 5.57 (m, 1H, CH), 6.33 (m, 2H, CH_2 , 6.62 (d, $J=9$ Hz, 1H, proton ortho to hydroxyl), 6.83 (d, $J=9$ Hz, 1H, proton ortho to allyloxy), 7.72 (t, $J=9$ Hz, 1H, proton para to acetyl).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.75; H, 6.25.
Found: C, 68.66; H, 6.54.

10 b) Preparation of 2,6-dihydroxy-3-allylacetophenone

- 2-hydroxy-5-allyloxyacetophenone (30 gm; 0.156 mole) was heated under nitrogen at 190°C for a period of 10 minutes. The mixture was cooled and taken up into carbon tetrachloride to yield 2,6-dihydroxy-3-allylacetophenone, mp $67-68^\circ\text{C}$ in quantitative yield.

- ^1H NMR 2.77 (s, 3H, CH_3), 3.37 (d, $J=6$ Hz, 2H, OCH_2), 5.37 (m, 1H, CH), 6.00 (m, 2H, CH_2 , 6.33 (d, $J=9$ Hz, 1H, proton ortho to hydroxyl), 7.17 (d, $J=9$ Hz, 1H, proton meta to hydroxy).

- Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.75; H, 6.25.
Found: C, 68.90; H, 6.21.

c) Preparation of 2,6-dihydroxy-3-propylacetophenone

- 2,6-dihydroxy-3-allylacetophenone (30 gm; 0.156 mole) dissolved in ethanol (150 mL) was hydrogenated in a Parr apparatus in presence of 5% palladium on carbon. The catalyst was removed by

2882P/1043A

2884P/1045A

- 99 -

171411A

filtration and the filtrate was concentrated to dryness to yield 30 gm of 2,6-dihydroxy-3-propyl-acetophenone, mp. 76-78°C.

- 5 ^1H NMR 0.97 (t, J = 7 Hz, 3H, CH_3), 1.60 (sextet, J=7 Hz, 2H, CH_2), 2.53 (t, J=7Hz, 2H, CH_2), 2.73 (s, 3H, CH_3), CH_2 , 6.30 (d, J=9Hz, 1H, proton ortho to hydroxy), 7.13 (d, J= 9 Hz, 1H, proton meta to hydroxy).

10

Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$: C, 68.04; H, 7.21.
Found: C, 68.05; H, 7.34.

- 15 d) Preparation of 2,6-dihydroxy-3-propyl-5-fluoro-acetophenone

- Method 1.) A solution of 2,6-dihydroxy-3-propyl-acetophenone (194 mg; 1 mmole) in Freon (fluoro-trichloromethane) (30 mL) was cooled at -78°C and
20 trifluoromethylhypofluorite was bubbled through the solution slowly, monitoring the reaction by TLC until about half of the material has reacted. The mixture is poured onto a silica gel column and elution with 15% ethylacetate in hexane gave 40 mg of
25 2,6-dihydroxy-3-propyl-5-fluoroacetophenone.

- ^1H NMR 0.93 (t, J = 7 Hz, 3H, CH_3), 1.67 (sextet, J=7 Hz, 2H, CH_2), 2.57 (t, J=7Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 6.18 (d, J=6 Hz, 1H, OH ortho to
30 fluoro), 7.13 (d, J=11 Hz, 1H, proton ortho to fluoro).

Method 2a.) Preparation of 2,6-dimethoxy-3-propyl-5-fluoroacetophenone

2882P/1043A

2884P/1045A

- 100 -

171411A

A solution of 2,6-dimethoxy-3-propylaceto-
phenone (21.0 gm; 94.6 mmoles) in Freon (30 mL) was
cooled at -78°C and trifluoromethylhypofluorite was
bubbled through the solution slowly, monitoring the
5 reaction by TLC until about 75% of the material has
reacted. The mixture is poured onto a silica gel
column and elution with 15% ethylacetate in hexane
gave 11.1 g of 2,6-dimethoxy-propyl-5-fluoroaceto-
phenone and 9.0 gm of unreacted 2,6-dimethoxy-3-
10 propylacetophenone .

^1H NMR 0.97 (t, $J = 7$ Hz, 3H, CH_3), 1.67 (sextet,
 $J = 7$ Hz, 2H, CH_2), 2.50 (t, $J = 7$ Hz, 2H, CH_2), 2.50
(s, 3H, CH_3), 3.70 (s, 3H, CH_3) 3.82 (d, $J = 3$
15 Hz, 3H, CH_3), 6.90 (d, $J = 11$ Hz, 1H, proton ortho to
fluoro).

2b.) Preparation of 2,6-dihydroxy-3-propyl-5-fluoro-
acetophenone

20

To a solution of 2,6-dimethoxy-3-propyl-5-
fluoroacetophenone (3.0 gm; 12.5 mmoles) in methylene
chloride (32 mL) cooled to -78°C , was added dropwise
over a period of 1 hour a 1M solution of boron
25 tribromide (56 mL; 56 mmoles) The temperature was
allowed to rise to room temperature and the reaction
mixture was stirred for 3 hours. It was then cooled
to -78°C and methanol (20 mL) was added rapidly. The
resulting solution was poured in water, the phases
30 were separated and the aqueous phase was extracted
with methylene chloride. The organic phases were
combined, washed with brine, dried (Na_2SO_4), and
concentrated in vacuo. The residue was chromato-

2882P/1043A

2884P/1045A

- 101 -

171411A

graphed on silica gel and eluted with 7% ethylacetate in hexane to yield 1.5 gm (58%) of 2,6-dihydroxy-3-propyl-5-fluoroacetophenone.

- 5 ^1H NMR 0.93 (t, $J = 7$ Hz, 3H, CH_3), 1.63 (sextet, $J = 7$ Hz, 2H, CH_2), 2.50 (t, $J = 7$ Hz, 2H, CH_2), 2.73 (s, 3H, CH_3), 5.93 (d, $J = 6$ Hz, 1H, OH), 7.10 (d, $J = 11$ Hz, 1H, proton ortho to fluoro).

- 10 e) Preparation of 2-carboethoxymethoxy-6-hydroxy-3-propyl-5-fluoroacetophenone

- 15 A mixture of 2,6-dihydroxy-5-fluoro-3-propyl-acetophenone (3.5 gm, 16.5 mmoles), ethyl bromoacetate (2.0 ml; 18.1 mmoles) and potassium carbonate (2.27 gm; 16.5 mmoles) in acetone (1 liter) was refluxed for a period of 0.5 hour. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo to yield a residue that
- 20 purified by chromatography on silica gel. Elution with 10 % ethyl acetate in hexane yielded 4.2 gm (86%) of 2-carboethoxymethoxy-6-hydroxy-3-propyl-5-fluoroacetophenone.

- 25 ^1H NMR 0.93 (t, $J = 7$ Hz, 3H, CH_3), 1.27 (t, $J = 7$ Hz, 3H, CH_3), 1.63 (sextet, $J = 7$ Hz, 2H, CH_2), 2.53 (t, $J = 7$ Hz, 2H, CH_2), 2.77 (s, 3H, CH_3), CH_2 , 4.20 (q, $J = 7$ Hz, 2H, CH_2O), 4.80 (s, 2H, CH_2), 7.03 (d, $J = 11$ Hz, 1H, proton ortho to fluoro).
- 30

2882P/1043A

2884P/1045A

- 102 -

171411A

f) Preparation of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran.

A solution of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (15 gm; 50.0 mmoles) in freshly-distilled absolute ethanol (0.5 liter) was brought to reflux and a 1M solution of sodium ethoxide (100 mL; 100 mmoles) was added rapidly. The reaction mixture was refluxed for a period of 1 hour. It was cooled to room temperature and poured into 0.5N hydrochloric acid and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), concentrated in vacuo, and the residue was chromatographed on silica gel. Elution with 10% ethylacetate in hexane yielded 9.0 gm of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran.

^1H NMR 1.00 (t, $J = 7$ Hz, 3H, CH_3), 1.43 (t, $J = 7$ Hz, 3H, CH_3), 1.63 (sextet, $J = 7$ Hz, 2H, CH_2), 2.57 (t, $J = 7$ Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 4.47 (q, $J = 7$ Hz, 2H, CH_2O), 4.97 (s, 1H, OH), 6.90 (s, 1H, proton ortho to fluoro).

3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran. (1.0 gm) mp. 53-54°C was also obtained.

^1H NMR 1.00 (t, $J = 7$ Hz, 3H, CH_3), 1.63 (sextet, $J = 7$ Hz, 2H, CH_2), 2.40 (d, $J = 2$ Hz, 3H, CH_3), 2.57 (t, $J = 7$ Hz, 2H, CH_2), 4.73 (s, 1H, OH), 6.73 (d, $J = 11$ Hz, 1H, proton ortho to fluoro), 7.28 (d, $J = 2$ Hz, 1H, H2).

Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 69.23; H, 6.25;
F, 9.13. Found: C, 64.14; H, 5.79; Cl, 15.81.

5 g) Preparation of 3-methyl-4-hydroxy-5-propyl-7-fluorobenzofurancarboxylic acid

To a solution of 2-carboethoxy-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (1.0 gm, 3.6 mmoles) in methanol (100 mL) was added 2N sodium hydroxide (10 mL) and the resulting solution was refluxed for a period of 4.5 hours. The reaction mixture was concentrated in vacuo. The residue was acidified with 3N hydrochloric acid and then extracted with ethylacetate. The organic phase was dried (Na_2SO_4), concentrated in vacuo, and 3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran-carboxylic acid (0.79 gm; 88%) was isolated by filtering the solid after suspending in hexane.

20 1H NMR 0.97 (t, J = 7 Hz, 3H, CH_3), 1.60 (sextet, J = 7 Hz, 2H, CH_2), 2.67 (t, J = 7 Hz, 2H, CH_2), 2.80 (s, 3H, CH_3), 6.90 (d, J = 11 Hz, 1H, proton ortho to fluoro), 7.00 (s, 2H, OH).

25 h) Preparation of 3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran

A mixture of 3-methyl-4-hydroxy-5-propyl-7-fluorobenzofurancarboxylic acid (0.10 gm; 0.4 mmoles) and copper (20 mg) in quinoline (50 mL) was refluxed for a period of 2.5 hours. The two phases were separated and the organic phase was dried (Na_2SO_4), and concentrated in vacuo. The residue

was purified by preparative TLC and eluted with 5% ethylacetate in hexane to yield 3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (62 mg ; 75%), identical to the product obtained from the cyclisation reaction described above in step f.

i) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-(p-methoxybenzoyloxy)-5-propyl-7-fluorobenzofuran

A solution of p-anisoyl chloride (2.70 gm; 15.5 mmoles) in ethylene dichloride (10 mL) was added slowly to a cooled suspension of aluminium chloride (3.0 gm; 21.8 mmoles) in ethylene dichloride (100 mL). After stirring for a period of 10 minutes, 3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (0.79 gm; 3.8 mmoles) in dichloroethylene (5 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 1 hour. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 10% ethylacetate in hexane to yield 1.18 gm (63%) of 2-(p-methoxybenzoyl)-3-methyl-4-(p-methoxybenzoyloxy)-5-propyl-7-fluorobenzofuran.

^1H NMR 0.90 (t, $J=7$ Hz, 3H, CH_3), 1.63 (sextet, $J=7$ Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.63 (t, $J=7$ Hz, 2H, CH_2), 3.90 (s, 6H, CH_3), 6.97 (d, $J=9$ Hz, 1H, proton ortho to methoxy), 7.03 (d, $J=9$ Hz,

2882P/1043A

2884P/1045A

- 105 -

171411A

1H, proton ortho to methoxy), 8.13 (d, J=9 Hz, 1H, proton ortho to methoxy), 8.23 (d, J=9 Hz, 1H, proton ortho to methoxy).

- 5 Anal. Calcd for $C_{20}H_{21}ClO_3$: C, 69.66; H, 6.13; F, 10.28.
 Found: C, 69.80; H, 6.18; F, 10.23.

j) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran

10

- To an ice-cold suspension of aluminium chloride (1.14 gm, 8.5 mmoles) in ether (100 mL) was added slowly lithium aluminium hydride (1.39 gm, 36 mmoles). After stirring for a period of 10 minutes, 15 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran (1.18 gm, 2.48 mmoles) in ether (10 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 10 minutes. It was cooled with an ice-bath and ice 20 was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with ether. The organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue 25 was chromatographed on silica gel and eluted with 10% ethyl acetate in hexane to yield 0.58 gm (71%) of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-fluorobenzofuran.

- 30 1H NMR 0.98 (t, J= 7 Hz, 3H, CH_3), 1.66 (sextet, J=7 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.55 (t, J=7Hz, 2H, CH_2), 3.78 (s, 6H, CH_3), 4.00 (s, 2H, CH_2), 6.67 (d, J=11 Hz, 1H, proton ortho to

2882P/1043A

2884P/1045A

- 106 -

17141IA

fluoro), 6.84 (d, 2H, proton ortho to methoxy), 7.16 (d, J=9 Hz, 1H, proton meta to methoxy).

Anal. Calcd for $C_{20}H_{21}ClO_3$: C, 73.15; H, 6.44;

5 F, 5.78. Found: C, 73.71; H, 6.45; F, 5.09.

EXAMPLE 26

10 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-7-propyl- benzofuran

a) Preparation of 2-hydroxy-3-propyl-6-benzyloxy-acetophenone

15 A mixture of 2,6-dihydroxy-3-propylaceto-
phenone (5.5 gm; 28.3 mmoles), potassium carbonate
(3.9 gm; 31 mmoles) and benzyl bromide (4.3 gm; 31
mmoles) in acetone (10 liters) was refluxed for a
period of twenty hours. The reaction mixture was
20 cooled, filtered through Celite, and concentrated in
vacuo. The residue was chromatographed on silica gel
using 10% ethylacetate in hexane as eluent to yield
5.6 gm (70%) of 2-hydroxy-3-propyl-6-benzyloxyaceto-
phenone.

25

1H NMR 0.93 (t, 3H, J = 7 Hz, CH_3), 1.60 (sextet,
2H, J = 7 Hz, CH_2), 2.60 (t, 2H, J = 7 Hz, CH_2),
2.67 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 6.40 (d,
1H, J = 9 Hz, H5), 7.23 (d, 1H, J = 9 Hz, H4), 7.40
30 (s, 5H, phenyl protons).

2882P/1043A

2884P/1045A

- 107 -

171411A

b) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-benzyloxy-7-propyl-benzofuran.

A mixture of 2-hydroxy-3-propyl-6-benzyloxy-acetophenone (1.0 gm; 3.52 mmoles), potassium carbonate (0.81 gm; 3.82 mmoles) and p-methoxyphenacyl bromide (0.54 gm, 3.80 mmoles) in methylethylketone (40 mL) was refluxed for a period of 20 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 10% ethylacetate in hexane as eluent to yield 0.74 gm (51%) of 2-(p-methoxybenzoyl)-3-methyl-4-benzyloxy-7-propylbenzofuran.

15

¹H NMR 0.93 (t, 3H, J = 7 Hz, CH₃), 1.67 (sextet, 2H, J = 7 Hz, CH₂), 2.75 (s, 3H, CH₃), 2.75 (t, 2H, J = 7 Hz, CH₂), 3.83 (s, 3H, CH₃), 5.13 (s, 2H, CH₂), 6.60 (d, 1H, J = 9 Hz, H5), 6.93 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.10 (d, 1H, J = 9 Hz, H6), 7.40 (s, 5H, phenyl protons), 8.10 (d, 2H, J = 9 Hz, protons meta to methoxy).

20

c) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-7-propylbenzofuran

25

A mixture of 2-(p-methoxybenzoyl)-3-methyl-4-benzyloxy-7-propylbenzofuran (0.10 gm, 0.24 mmole) in ethanol was hydrogenated in a Parr hydrogenator in the presence of 10% palladium on charcoal at 40 psi for a period of 7 hours. The catalyst was filtered off, washed with some ethanol, and the filtrate was concentrated in vacuo to yield 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-7-propylbenzofuran.

30

2882P/1043A

2884P/1045A

- 108 -

17141IA

¹H NMR 0.90 (t, 3H, J = 7 Hz, CH₃), 1.63 (sextet, 2H, J = 7 Hz, CH₂), 2.33 (s, 3H, CH₃), 2.70 (t, 2H, J = 7 Hz, CH₂), 3.73 (s, 3H, CH₃), 3.93 (s, 2H, CH₂), 4.97 (s, 1H, OH), 6.37 (d, 1H, J = 9 Hz, H5), 6.78 (d, 2H, J = 9 Hz, protons ortho to methoxy), (d, 1H, J = 9 Hz, H6), 7.17 (d, 2H, J = 9 Hz, protons meta to methoxy).

EXAMPLE 27

10

2-(p-methoxybenzyl)-3-methyl-4-propyl-5-hydroxy-benzofuran

15 a) Preparation of 2-(p-methoxybenzoyl)-3-methyl-5-allyloxybenzofuran.

A mixture of 2-hydroxy-5-allyloxyacetophenone (7.7 gm; 40.0 mmoles), potassium carbonate (6.90 gm; 50.0 mmoles) and p-methoxyphenacyl bromide (11.4 gm, 50.0 mmoles) in acetone (100 mL) was
20 refluxed for a period of 22 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 50% ethylacetate in
25 hexane as eluent to yield 7.2 gm (56%) of 2-(p-methoxybenzoyl)-3-methyl-5-allyloxybenzofuran, mp. 74-76°C.

¹H NMR 2.60 (s, 3H, CH₃), 3.88 (s, 3H, CH₃),
30 4.60 (m, 2H, CH₂), 5.40 (m, 2H, CH₂), 6.10 (m, 1H, CH), 7.10 (m, 4H, protons ortho to methoxy, H4 and H6), 7.43 (1H, J = 9 Hz, H7), 8.17 (d, 2H, J = 9 Hz, protons ortho to methoxy).

2882P/1043A

2884P/1045A

- 109 -

171411A

b) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-allyl-5-hydroxybenzofuran

A mixture of 2-(p-methoxybenzoyl)-3-methyl-5-allyloxybenzofuran (1 gm, 3.10 mmole) in ortho dichlorobenzene (5 mL) was refluxed under nitrogen for a period of 5 hours. On cooling, the product crystallized. It was diluted with hexane, filtered, washed with hexane, and air-dried to yield 870 mg (87%) of 2-(p-methoxybenzoyl)-3-methyl-4-allyl-5-hydroxy-benzofuran, mp. 155-158°C.

¹H NMR 2.68 (s, 3H, CH₃), 3.80 (m, 5H, CH₃ and CH₂), 5.00 (m, 2H, CH₂), 6.03 (m, 1H, CH), 6.90 (d, 3H, protons ortho to methoxy-and H6), 7.23 (1H, J = 9 Hz, H7), 8.03 (d, 2H, J = 9 Hz, protons ortho to methoxy).

c) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran

A solution of 2-(p-methoxybenzoyl)-3-methyl-4-allyl-5-hydroxybenzofuran (3 gm, 9.3 mmoles) in ethanol (150 mL) was hydrogenated in a Parr hydrogenator in the presence of 10% palladium on charcoal at 40 psi for a period of 3 hours. The catalyst was filtered off, washed with some ethanol, and the filtrate was concentrated in vacuo. The residue was recrystallized from hexane to yield (1.1 gm, 38%) of 2-(p-methoxybenzyl)-3-methyl-4-propyl-5-hydroxybenzofuran, mp. 91-93°C.

2882P/1043A

2884P/1045A

- 110 -

171411A

¹H NMR 1.00 (t, 3H, J = 7 Hz, CH₃), 1.63 (sextet, 2H, J = 7 Hz, CH₂), 2.33 (s, 3H, CH₃), 2.87 (t, 2H, J = 7 Hz, CH₂), 3.73 (s, 3H, CH₃), 3.93 (s, 2H, CH₂), 4.37 (s, 1H, OH), 6.63 (d, 1H, J = 9 Hz, H6), 6.78 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.07 (d, 1H, J = 9 Hz, H7), 7.13 (d, 2H, protons meta to methoxy).

EXAMPLE 282-(p-methoxybenzyl)-3-methyl-4-hydroxybenzofuran

a) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxybenzofuran

A mixture of 2,6-dihydroxyacetophenone (5.35 gm; 35.0 mmoles), potassium carbonate (4.83 gm; 35.0 mmoles), and p-methoxyphenacylbromide (8.05 gm; 35.0 mmoles) in acetone (150 mL) was refluxed for a period of 22 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was dissolved in methylene chloride and washed with 1N sodium hydroxide. The aqueous phase was then acidified with 20% citric acid. The solid was filtered, washed with water, and air-dried to yield 6.5 gm (65%) of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxybenzofuran, mp. 192-195°C.

¹H NMR 2.80 (s, 3H, CH₃), 3.90 (s, 3H, CH₃), 6.73 (d, 1H, J = 9 Hz, H5), 7.07 (m, 4H, protons ortho to methoxy, H5 and H6), 8.13 (d, J = 9Hz, 2H, proton ortho to carbonyl).

2882P/1043A

2884P/1045A

- 111 -

171411A

b) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-hydroxybenzofuran

A mixture of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxybenzofuran (2.0 gm; 7.0 mmoles), 99% hydrazine (50 mL) and potassium hydroxide (2.7 gm; 49 mmoles) in ethylene glycol (50 mL) was heated at 140°C for a period of 2.5 hours and at 195°C for one hour. The reaction mixture was cooled, poured in water, and extracted with ethylacetate. The organic phase was washed with 20% citric acid, with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethylacetate in hexane as eluent to yield 700 gm (37%) of 2-(p-methoxybenzyl)-3-methyl-4-hydroxybenzofuran, mp. 130-133°C.

^1H NMR 2.40 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 5.04 (s, 1H, OH), 6.48 (d, 2H, J=9 Hz, H5), 6.88 (m, 4H, protons ortho to methoxy, H6 and H7), 7.15 (d, J=9 Hz, 2H, proton meta to methoxy).

Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3$: C, 76.09; H, 6.01;
Found: C, 76.21; H, 6.39.

EXAMPLE 29

2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propylbenzofuran

a) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-allyloxybenzofuran

2882P/1043A

2884P/1045A

- 112 -

17141IA

A mixture of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxybenzofuran (0.60 gm; 2.2 mmoles), potassium carbonate (0.83 gm; 6.0 mmoles) and allyl bromide (0.73 gm; 6.0 mmoles) in acetone (25 mL) was refluxed for a period of 22 hours. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethylacetate in hexane as eluent to yield 2-(p-methoxybenzoyl)-3-methyl-4-allyloxybenzofuran.

10

^1H NMR 2.40 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 4.64 (m, 2H, CH_2), 5.40 (m, 2H, CH_2), 6.12 (m, 1H, CH), 6.60 (d, 1H, $J = 9$ Hz, H5), 6.84 (d, 2H, $J = 9$ Hz, protons ortho to methoxy), 7.00 (d, 1H, $J = 9$ Hz, H7), 7.06 (d, 1H, $J = 9$ Hz, H6), 7.15 (d, $J = 9$ Hz, 2H, proton meta to methoxy).

15

Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3$: C, 77.89; H, 6.53;
Found: C, 77.87; H, 6.76.

20

b) Preparation of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-allylbenzofuran

A solution of 2-(p-methoxybenzoyl)-3-methyl-4-allyloxybenzofuran (0.7 gm; 2.2 mmoles) in ortho-dichlorobenzene (3 mL) was refluxed under nitrogen for a period of 4 hours. The mixture was cooled to room temperature and purified by chromatography on silica gel using 15% ethylacetate in hexane as eluent to yield 650 mg (93%) of 2-(p-methoxybenzoyl)-3-methyl-4-hydroxy-5-allylbenzofuran, mp. 48-50°C.

25

30

2882P/1043A

2884P/1045A

- 113 -

171411A

- ^1H NMR 2.41 (s, 3H, CH_3), 3.44 (m, 2H, CH_2),
3.78 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 5.23 (m,
2H, CH_2), 6.03 (m, 1H, CH), 6.84 (d, 2H, $J = 9$ Hz,
protons ortho to methoxy), 6.88 (s, 2H, H6 and H7),
5 7.15 (d, $J = 9$ Hz, 2H, proton meta to methoxy).

Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3$: C, 77.89; H, 6.53;
Found: C, 77.80; H, 6.81.

- 10 c) Preparation of 2-(p-methoxybenzyl)-3-methyl-4-
hydroxy-5-propylbenzofuran.

- A solution of 2-(p-methoxybenzoyl)-3-methyl-
4-hydroxy-5-allylbenzofuran (40 mg) in ethanol (50
15 mL) was hydrogenated in a Parr hydrogenator in the
presence of 10% palladium on charcoal at 40 psi. The
catalyst was filtered and the filtrate was concen-
trated to dryness to yield 2-(p-methoxybenzyl)-3-
methyl-4-hydroxy-5-propylbenzofuran, identical to the
20 product prepared by the route described in Example 1.

EXAMPLE 30

- 2-benzyl 3-methyl-4-hydroxy-5-propyl-7-chloro-
25 benzofuran

- a) Preparation of 2-benzoyl-3-methyl-4-benzoyloxy-
5-propyl-7-chlorobenzofuran

- 30 A solution of benzoyl chloride (3.03 gm;
21.6 mmoles) in ethylene dichloride (20 mL) was added
slowly to a cooled suspension of aluminium chloride
(5.8 gm; 43 mmoles) in ethylenedichloride (100 mL).

2882P/1043A

2884P/1045A

- 114 -

17141IA

After stirring for a period of 10 minutes, 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (1.62 gm; 7.2 mmoles) in dichloroethylene (20 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 1 hour. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 10% ethylacetate in hexane to yield 1.18 gm (63%) of 2-benzoyl-3-methyl-4-benzoyloxy-5-propyl-7-chlorobenzofuran, mp. 141-142°C.

^1H NMR 0.93 (t, $J=7$ Hz, 3H, CH_3), 1.63 (sextet, $J=7$ Hz, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.60 (t, $J=7$ Hz, 2H, CH_2), 7.33 (s, 1H, H6), 7.50 (m, 6H, meta and para protons of benzoyl group), 8.20 (m, 4H, protons ortho to carbonyl).

Anal. Calcd for $\text{C}_{26}\text{H}_{21}\text{ClO}_4$: C, 72.13; H, 4.88; Cl, 8.18.
Found: C, 71.30; H, 5.05; Cl, 8.37.

b) Preparation of 2-benzyl-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

To an ice-cold suspension of aluminium chloride (2.50 gm, 18 mmoles) in ether (300 mL) was added slowly lithium aluminium hydride (3.0 gm, 80 mmoles). After stirring for a period of 10 minutes,

2882P/1043A

2884P/1045A

- 115 -

17141IA

2-benzyl-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (2.31 gm, 5.33 mmoles) in ether (10 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 10 minutes. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with ether. The organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 10% ethylacetate in hexane to yield 1.30 gm (77%) of 2-benzyl-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, mp. 69-70°C.

^1H NMR 0.98 (t, $J=7$ Hz, 3H, CH_3), 1.60 (sextet, $J=7$ Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.63 (t, $J=7$ Hz, 2H, CH_2), 4.00 (s, 2H, CH_2), 4.80 (s, 1H, OH), 6.90 (s, 1H, H6), 7.23 (s, 5H, phenyl protons).

Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{ClO}_2$: C, 72.49; H, 6.08; Cl, 11.26.
Found: C, 72.48; H, 6.16; Cl, 11.02.

EXAMPLE 31

2-(p-hydroxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

To a solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (100 mg, 0.29 mmole) in methylene chloride (5 mL) cooled to -78°C, was added dropwise over a period of 5 minutes a 1M solution of boron tribromide (0.3mL; 0.3 mmole)

2882P/1043A

2884P/1045A

- 116 -

171411A

in methylene chloride. The temperature was allowed to rise to room temperature and the reaction mixture was stirred for 3 hours. It was then cooled to -78°C and methanol (2 mL) was added rapidly. The resulting solution was poured into water. The phases were separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 15% ethyl acetate in hexane to yield 63 mg gm (66%) of 2-(p-hydroxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, mp. $142-143^{\circ}\text{C}$.

15

EXAMPLE 32

2-(p-bromobenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

20 a) Preparation of 2-(p-bromobenzoyl)-3-methyl-4-(p-bromobenzoyloxy)-5-propyl-7-chlorobenzofuran

A solution of p-bromobenzoyl chloride (1.1 gm; 5.0 mmoles) in ethylene dichloride (5 mL) was added slowly to a cooled suspension of aluminium chloride (3.3 gm; 25 mmoles) in ethylene dichloride (75 mL). After stirring for a period of 10 minutes, 3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (0.95 gm; 4.2 mmoles) in dichloroethylene (20 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 1 hour. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was

2882P/1043A

2884P/1045A

- 117 -

171411A

separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 10% ethylacetate in hexane to yield 260 mg gm of 2-(p-bromobenzoyl-3-methyl-4-(p-bromobenzoyloxy)-5-propyl-7-chlorobenzofuran.

^1H NMR 0.97 (t, $J = 7$ Hz, 3H, CH_3), 1.70 (sextet, $J = 7$ Hz, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.63 (t, $J = 7$ Hz, 2H, CH_2), 7.43 (s, 1H, H6), 7.80 (m, 4H, protons meta to carbonyl), 8.20 (m, 4H, protons ortho to carbonyl).

b) Preparation of 2-(p-bromobenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

To an ice-cold suspension of aluminium chloride (0.5 gm, 3.6 mmoles) in ether (100 mL) was added slowly lithium aluminium hydride (1.0 gm, 26.7 mmoles). After stirring for a period of 10 minutes, 2-(p-bromobenzyl)-3-methyl-4-(p-bromobenzoyloxy)-5-propyl-7-chlorobenzofuran (0.22 gm, 0.37 mmole) in ether (10 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 10 minutes. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with ether. The organic phases were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 10% ethyl acetate in hexane to yield 178 mg (97%) of

2882P/1043A

2884P/1045A

- 118 -

17141IA

2-benzyl-3-methyl-4-hydroxy-5-propyl-7-chloro-
benzofuran.

¹H NMR 0.98 (t, J = 7 Hz, 3H, CH₃), 1.57 (sextet, J = 7 Hz, 2H, CH₂), 2.33 (s, 3H, CH₃), 2.53 (t, J = 7 Hz, 2H, CH₂), 3.98 (s, 2H, CH₂), 4.80 (s, 1H, OH), 6.93 (s, 1H, H₆), 7.10 (d, 2H, J = 9 Hz, protons ortho to bromo), 7.33 (d, 2H, J = 9 Hz, protons meta to bromo).

10

EXAMPLE 33

2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-propyl-
7-chlorobenzofuran

15

a) Preparation of 2-(p-methoxyphenacetyl)-3-methyl-
4-(p-methoxyphenacetyloxy)-5-propyl-7-chlorobenzo-
furan

20

A solution of p-methoxyphenacetyl chloride (2.0 gm; 11 mmoles) in ethylene dichloride (5 mL) was added slowly to a cooled suspension of aluminium chloride (2.9 gm; 22 mmoles) in ethylene dichloride (145 mL). After stirring for a period of 10 minutes,

25

3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (0.87 gm; 3.6 mmoles) in dichloroethylene (20 mL) was added over a period of 2 minutes. The reaction mixture was stirred at room temperature for 1 hour. It was cooled with an ice-bath and ice was added slowly.

30

When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with methylene chloride. The organic phases were combined, dried (Na₂SO₄), and

2882P/1043A

2884P/1045A

- 119 -

171411A

concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 15% ethylacetate in toluene to yield 1.3 gm of 2-(p-methoxyphenacetyl)-3-methyl-4-(p-methoxyphenacetyloxy)-5-propyl-7-chlorobenzofuran.

¹H NMR 0.83 (t, J = 7 Hz, 3H, CH₃), 1.50 (sextet, J = 7 Hz, 2H, CH₂), 2.40 (s, 3H, CH₃), 2.40 (t, J = 7 Hz, 2H, CH₂), 3.80 (m, 10H, CH₃ and CH₂), 6.80 (m, 4H, protons ortho to methoxy), 7.2 (m, 5H, H6 and protons meta to methoxy).

b) Preparation of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

15

To a solution of 2-(p-methoxyphenacetyl)-3-methyl-4-(p-methoxyphenacetyloxy)-5-propyl-7-chlorobenzofuran (0.76 gm, 1.4 mmoles) in tetrahydrofuran (25 mL) was added a solution of 1M diborane in tetrahydrofuran (5 mL; 5 mmoles). The reaction was stirred at room temperature for 30 minutes. Methanol was then added and the volatiles were removed in vacuo to yield a residue that was taken up in tetrahydrofuran (25 mL) and added to a mixture of aluminium chloride (0.67 gm, 4 mmoles) and lithium aluminium hydride (0.80 gm, 21 mmoles) in tetrahydrofuran (25 mL). The mixture was stirred at room temperature for 2 hours and was refluxed for 15 minutes. It was cooled with an ice-bath and ice was added slowly. When the vigorous reaction subsided, the organic layer was separated and the aqueous phase was extracted with ether. The organic phases were combined, washed with brine, dried (Na₂SO₄), and

25

30

2882P/1043A

2884P/1045A

- 120 -

171411A

concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 15% ethyl acetate in hexane to yield 100 mg (20%) of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran.

^1H NMR 0.98 (t, $J=7$ Hz, 3H, CH_3), 1.63 (sextet, $J=7$ Hz, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.58 (t, $J=7$ Hz, 2H, CH_2), 2.98 (s, 4H, CH_2), 3.80 (s, 2H, CH_2), 4.80 (s, 1H, OH), 6.80 (d, 2H, $J=9$ Hz, protons ortho to methoxy), 6.88 (s, 1H, H6), 7.03 (d, 2H, $J=9$ Hz, protons meta to methoxy).

EXAMPLE 34

15

2-(p-methoxyphenethyl)-3-methyl-4-hydroxybenzofuran

a) Preparation of 3-methyl-4-acetoxymethylbenzofuran

A solution of 3-methyl-4-hydroxybenzofuran (5.0 gm, 34.7 mmols), acetic anhydride (50 mL) and triethylamine (25 mL) in tetrahydrofuran (150 mL) was stirred at room temperature overnight. The volatiles were removed in vacuo and the residue was purified by chromatography on silica gel. Elution with 15% ethylacetate in hexane yielded 3-methyl-4-acetoxymethylbenzofuran.

^1H NMR 2.17 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.88 (d of d, 1H, H5), 7.20 (m, 3H, H2, H6 and H7).

2882P/1043A

2884P/1045A

- 121 -

171411A

b) Preparation of 2-E-(1-(p-methoxyphenyl)-vinyl)-3-methyl-4-acetoxybenzofuran

A mixture of 3-methyl-4-acetoxybenzofuran (3.7 gm, 19.4 mmoles), palladium (II) acetate (5.6 gm, 25 mmoles), and p-methoxystyrene (6.7 gm, 50 mmoles) in acetic acid (100 mL) was refluxed for 45 minutes. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was slurried with hexane, the insolubles were decanted, and the hexane solution was left to crystallize. The solid was filtered, washed with hexane, and air-dried to yield 1.6 gm (26%) 2-E-(1-(p-methoxyphenyl)-vinyl)-3-methyl-4-acetoxybenzofuran, mp. 146-148°C.

^1H NMR 2.30 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 7.10 (m, 9H, aromatic protons and vinyl protons).

c) Preparation of 2-(p-methoxyphenethyl)-3-methyl-4-acetoxybenzofuran

A solution of 2-E-(1-(p-methoxyphenyl)-vinyl)-3-methyl-4-acetoxybenzofuran (1.29 gm, 4 mmoles) in ethanol (75 mL) was hydrogenated in a Parr hydrogenator in the presence of 5% palladium on charcoal at 50 psi for a period of 2 hours. The catalyst was filtered off and the filtrate was concentrated in vacuo to yield 1.26 gm (98%) of 2-(p-methoxyphenethyl)-3-methyl-4-acetoxybenzofuran, mp. 66-69°C.

2882P/1043A

2884P/1045A

- 122 -

171411A

^1H NMR 2.10 (s, 3H, CH_3), 2.37 (s, 3H, CH_3),
2.97 (s, 4H, CH_2), 3.80 (s, 3H, CH_3), 7.10 (m,
7H, aromatic protons).

5 d) Preparation of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxybenzofuran

A solution of 2-(p-methoxyphenethyl)-3-methyl-4-acetoxy-benzofuran (1 gm, 3 mmoles) in
10 methanol (50 mL) and 1N sodium hydroxide (10 mL) was
stirred at room temperature for a period of 10
minutes. The mixture was acidified with 20% citric
acid and the volatiles were removed in vacuo. The
aqueous residue was extracted with ether, washed with
15 water, dried (Na_2SO_4), filtered, and concentrated
to yield a residue that was chromatographed on silica
gel. Elution with 15% ethylacetate in hexane yielded
2-(p-methoxyphenethyl)-3-methyl-4-hydroxybenzofuran,
mp. 72-75°C.

20

^1H NMR 2.20 (s, 3H, CH_3), 2.97 (s, 4H, CH_2),
3.80 (s, 3H, CH_3), 6.90 (m, 7H, aromatic protons).

EXAMPLE 35

25

2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-propyl-
benzofuran

30

a) Preparation of 2-(p-methoxyphenethyl)-3-methyl-
4-allyloxybenzofuran

A mixture of 2-(p-methoxyphenethyl)-3-methyl-
4-hydroxybenzofuran (1.3 gm; 4.6 mmoles), potassium

2882P/1043A

2884P/1045A

- 123 -

17141IA

carbonate (1.38 gm, 10 mmoles), and allyl bromide (1.2 gm, 10 mmoles) in acetone (50 mL) was refluxed for a period of 5 hours. The solids were filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel and eluted with 15% ethylacetate in hexane to yield 0.9 gm of 2-(p-methoxyphenethyl)-3-methyl-4-allyloxybenzofuran, which was used as such for the next step.

10 b) Preparation of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-allylbenzofuran

A solution of 2-(p-methoxyphenethyl)-3-methyl-4-allyloxybenzofuran (0.9 gm, 2.8 mmoles) in ortho dichlorobenzene (15 mL) was refluxed for 4.5 hours under a nitrogen atmosphere. The mixture was cooled to room temperature and was chromatographed on silica gel. Elution with 15% ethylacetate in hexane yielded 0.6 gm (67%) of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-allylbenzofuran.

¹H NMR 2.10 (s, 3H, CH₃), 2.93 (s, 4H, CH₂), 3.40 (m, 2H, CH₂), 3.73 (s, 3H, CH₃), 5.17 (m, 2H, CH₂), 6.00 (m, 1H, CH), 6.73 (d, 2H, J = 9 Hz, protons ortho to methoxy), 6.87 (s, 2H, H6 and H7), 7.08 (d, 2H, protons meta to methoxy).

c) Preparation of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-propylbenzofuran

A solution of 2-(p-methoxyphenethyl)-3-methyl-4-hydroxy-5-allylbenzofuran (0.65 gm, 2 mmoles) in ethanol (50 mL) was hydrogenated in a Parr

2882P/1043A

2884P/1045A

- 124 -

17141IA

hydrogenator in the presence of 5% palladium on charcoal at 50 psi for a period of 2 hours. The catalyst was filtered off and the filtrate was concentrated in vacuo to yield 2-(p-methoxyphenethyl) 3-methyl-4-hydroxy-5-propylbenzofuran, mp 77-79°C.

¹H NMR 0.93 (t, 3H J = 7 Hz, CH₃), 1.60 (sextet, 2H, J = 7 Hz, CH₂), 2.17 (s, 3H, CH₃), 2.57 (t, 2H, J = 7 Hz, CH₂), 2.90 (s, 4H, CH₂), 3.73 (s, 3H, CH₃), 4.80 (s, 1H, OH), 6.73 (d, 2H, J = 9 Hz, protons ortho to methoxy), 6.87 (s, 2H, H6 and H7), 7.03 (d, 2H, protons meta to methoxy).

EXAMPLE 36

15

2-Benzyl-3-methyl-4,5-dihydroxybenzofuran

a) Preparation of 3-(3,4-methylenedioxyphenoxy)-4-phenyl-2-butanone

20

A mixture of sesamol (3,4-methylenedioxy phenol) (0.69 gm, 5 mmoles), 1-chloro-1-acetyl-2-phenethyl-1-triphenylphosphonium chloride (2.4 gm, 5 mmoles), and potassium carbonate (2.76 gm; 20 mmoles) in methylethylketone (50 mL) was refluxed for a period of 3 hours. More phosphonium salt was then added (0.4 gm, 0.84 mmoles) and reflux was continued for another 3 hours. The reaction mixture was cooled, filtered through Celite and concentrated in vacuo.

30 The residue was chromatographed on silica gel and eluted with 20% ethylacetate in hexane to yield 629 mg (46%) of 3-(3,4-methylenedioxyphenoxy)-4-phenyl-2-butanone as an oil.

2882P/1043A

2884P/1045A

- 125 -

171411A

^1H NMR 2.10 (s, 3H, CH_3), 3.10 (d, 2H, $J = 7$ Hz, CH_2), 4.63 (t, 1H, $J = 7$ Hz, CH), 5.90 (s, 2H, CH_2), 6.2 (d of d, 1H, $J = 9$ Hz, 3 Hz, HH6), 6.43 (d, 1H, $J = 3$ Hz, H2), 6.67 (d, 1H, $J = 9$ Hz, H5).

5

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_4$: C, 71.86; H, 5.67. Found: C, 71.92; H, 5.88.

10 b) Preparation of 2-benzyl-3-methyl-5,6-methylene-dioxybenzofuran

A mixture of 3-(3,4-methylenedioxyphenoxy)-4-phenyl-2-butanone (0.70 gm, 2.45 mmoles) in polyphosphoric acid (3.5 gm) was stirred by hand until the initial exothermic reaction subsided. The mixture was stirred in ice/water and the solid was collected, washed with water, and dried in vacuo. The solid was chromatographed on silica gel and eluted with 20% ethylacetate in hexane to yield 479 mg (73%) of 2-benzyl-3-methyl-5,6-methylene-dioxybenzofuran.

20

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_3$: C, 76.68; H, 5.30. Found: C, 76.55; H, 5.24.

25

c) Preparation of 2-benzyl-3-methyl-5,6-dihydroxybenzofuran

A solution of 2-benzyl-3-methyl-5,6-methylenedioxybenzofuran (226 mg, 0.85 mmole) in methylene chloride (10 mL) was cooled at -65°C and a 1M solution of boron tribromide in methylene chloride (0.85 mL) was added dropwise. The mixture was

30

2882P/1043A

2884P/1045A

- 126 -

17141IA

allowed to warm up to -25°C and was kept in that range for 1 hour. Methanol (5 mL) was then added and the mixture was evaporated in vacuo. The residue was chromatographed on silica gel and eluted with 25% ethylacetate in hexane to yield 128 mg of 2-benzyl-3-methyl-5,6-dihydroxybenzofuran, mp. $95.5-98^{\circ}\text{C}$.

^1H NMR 2.15 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 6.88 (s, 1H, H4), 6.95 (s, 1H, H7), 7.23 (m, 5H, phenyl).

EXAMPLE 37

2-(p-carboxymethoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

a) Preparation of 2-(p-acetoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran

A solution of 2-(p-hydroxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (1 gm; 3 mmoles) in pyridine (15 mL) and acetic anhydride (3 mL) was stirred at 50°C for 15 minutes. The volatiles were removed in vacuo leaving a residue that crystallised on cooling. It was slurried with hexane, filtered, washed with hexane, and air-dried to yield 1.1 gm (87%) of 2-(p-acetoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran, mp. $119-120^{\circ}\text{C}$.

^1NMR : 0.93 (t, 3H, $J = 7$ Hz, CH_3), 1.60 (sextet, 2H, $J = 7$ Hz, CH_2), 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.37 (t, 2H, $J = 7$

2882P/1043A

2884P/1045A

- 127 -

171411A

Hz, CH₂), 4.00 (s, 2H, CH₂), 7.00 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.07 (s, 1H, H₆), 7.20 (d, 2H, J = 9 Hz, protons meta to methoxy).

- 5 b) Preparation of 2-(p-hydroxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran

 A solution of 2-(p-acetoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran (150 mg, 0.36 mmole) in methanol (5 mL) and a saturated solution of potassium carbonate (3 mL) was stirred at room temperature for 5 minutes. The reaction was poured in water, extracted with methylene chloride, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to yield 107 mg (79%) of 2-(p-hydroxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran.

¹NMR: 0.93 (t, 3H, J = 7 Hz, CH₃), 1.60 (sextet, 2H, J = 7 Hz, CH₂), 2.18 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 2.50 (t, 2H, J = 7 Hz, CH₂), 3.97 (s, 2H, CH₂), 5.20 (s, 1H, OH), 6.67 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.03 (s, 1H, H₆), 7.07 (d, 2H, J = 9 Hz, protons meta to methoxy).

- 25 c) Preparation of 2-(p-carboethoxymethoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran

 A mixture of 2-(p-hydroxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran (107 mg; 0.28 mmole), ethylbromoacetate (100 mg, 0.60 mmole), potassium carbonate (100 mg, 0.73 mmole) in acetone (10 mL) was refluxed for 30 minutes. The solids were filtered off, the filtrate was concentrated in vacuo

2882P/1043A

2884P/1045A

- 128 -

17141IA

to yield a residue that was purified by chromatography on silica gel. Elution with 20% ethylacetate in hexane yielded 133 (100%) of 2-(p-carboethoxymethoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran.

¹NMR: 0.93 (t, 3H, J = 7 Hz, CH₃), 1.33 (t, 3H, J = 7 Hz, CH₃), 1.60 (sextet, 2H, J = 7 Hz, CH₂), 2.18 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 2.50 (t, 2H, J = 7 Hz, CH₂), 4.00 (s, 2H, CH₂), 4.23 (q, 2H, J = 7 Hz, CH₂), 4.53 (s, 2H, CH₂), 6.83 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.10 (s, 1H, H6), 7.23 (d, 2H, J = 9 Hz, protons meta to methoxy).

15 e) Preparation of 2-(p-carboxymethoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

A solution of 2-(p-carboethoxymethoxybenzyl)-3-methyl-4-acetoxy-5-propyl-7-chlorobenzofuran (133 mg; 0.28 mmole) in methanol (10 mL) and 10N sodium hydroxide (1 mL) was stirred at room temperature for a period of 30 minutes. Water was then added and the mixture was acidified with 6N hydrochloric acid. The solid was filtered, washed with water, and air-dried to yield 93 mg (82%) of 2-(p-carboxymethoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, mp. 179-180°C.

¹NMR: 1.00 (t, 3H, J = 7 Hz, CH₃), 1.67 (sextet, 2H, J = 7 Hz, CH₂), 2.43 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 4.60 (s, 2H, CH₂), 6.87 (d, 2H, J = 9 Hz, protons ortho to methoxy), 6.93 (s, 1H, H6), 7.20 (d, 2H, J = 9 Hz, protons meta to methoxy).

2882P/1043A

2884P/1045A

- 129 -

171411A

EXAMPLE 382-(p-methoxybenzyl)-3-methyl-4-succinyloxy-5-propyl-7-chlorobenzofuran

5

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (0.5 gm, 1.45 mmole), 0.58 succinic anhydride (0.58 gm, 5.8 mmoles), and triethylamine (0.58 gm, 5.8 mmoles) in tetrahydrofuran (15 mL) was refluxed overnight. The volatiles were removed in vacuo and the residue was purified by chromatography on silica gel. Elution with 15% ethylacetate in hexane containing also 5% acetic acid yielded 0.45 gm (69%) of 2-(p-methoxybenzyl)-3-methyl-4-succinyloxy-5-propyl-7-chlorobenzo-

15 furan, mp. 151-152°C.

¹NMR: 10.93(t, 3H, J = 7 Hz, CH₃), 1.60 (sextet, 2H, J = 7 Hz, CH₂), 2.27 (s, 3H, CH₃), 2.57 (s, 3H, CH₃), 2.90 (m, 4H, CH₂), 3.80 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 6.83 (d, 2H, J = 9 Hz, protons ortho to methoxy), 7.07 (s, 1H, H₆), 7.20 (d, 2H, J = 9 Hz, protons meta to methoxy).

20

25

EXAMPLE 392-(p-carboethoxymethoxybenzyl)-3-methyl-4-carboethoxymethoxy-5-propyl-7-chlorobenzofuran

30

A mixture of 2-(p-hydroxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (483 mg; 1.46 mmole), ethylbromoacetate (325 mg, 1.90 mmole), and potassium carbonate (500 mg, 3.62 mmoles) in acetone

2882P/1043A

2884P/1045A

- 130 -

171411A

(20 mL) was refluxed for 60 minutes. The solids were filtered off. The filtrate was concentrated in vacuo to yield a residue that was purified by chromatography on silica gel. Elution with 20% ethylacetate in hexane yielded 520 (85%) of 2-(p-carboethoxy-methoxybenzyl)-3-methyl-4-carboethoxymethoxy-5-propyl-7-chlorobenzofuran.

¹NMR: 0.93 (t, 3H, J = 7 Hz, CH₃), 0.98 (t, 3H, J = 7 Hz, CH₃), 1.33 (t, 3H, J = 7 Hz, CH₃), 1.60 (sextet, 4H, J = 7 Hz, CH₂), 2.33 (t, 4H, J = 7 Hz, CH₂), 4.00 (q, 2H, J = 7 Hz, CH₂), 4.18 (s, 2H, CH₂), 4.30 (s, 2H, CH₂), 6.57 (d, 2H, J = 9 Hz, protons ortho to methoxy), 6.67 (s, 1H, H₆), 6.90 (d, 2H, J = 9 Hz, protons meta to methoxy).

EXAMPLE 40

20 O-sulfate of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran, ammonium salt

A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (5 gm, 14.5 mmoles) was added at 0°C to a mixture of diethyl aniline (4.3 ml) and chlorosulfonic acid (1 ml) in carbon disulfide (50 ml). The temperature was allowed to rise to room temperature and after 15 minutes, it was refluxed for 15 minutes. The reaction mixture was evaporated to dryness and the residue was purified by preparative thin layer chromatography. Eluting with a mixture of methanol, chloroform and ammonium hydroxide in the ratio of 4:8:1 (v/v/v) yielded 5 gm of the sulfate ester of

2882P/1043A

2884P/1045A

- 131 -

171411A

2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran as its ammonium salt; m.p.: 207-209°C.

- 5 ¹NMR: 0.93 (t, 3H, J=7 Hz, CH₃), 1.70 (sextet, 2H, J=7 Hz, CH₂), 2.47 (s, 3H, CH₃), 2.97 (t, J=7 Hz, 2H, CH₂), 3.70 (s, 3H, CH₃), 4.03 (s, 2H, CH₂), 6.83 (d, 2H, J=9 Hz, protons ortho to methoxy), 7.10 (d, 2H, J=9 Hz, protons meta to methoxy), 7.27 (s, 1H, H₆).
- 10

EXAMPLE 41

O-phosphate of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran

- 15 A solution of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran (5 gm, 14.5 mmoles) in chloroform (25 ml) was added at 0°C to a solution of phosphorus oxychloride (75 ml) in pyridine (25 ml) and acetone (250 ml). The mixture
- 20 was stirred at room temperature for a period of 1 hour and refluxed for 2 hours. The reaction mixture was evaporated to dryness and the residue was slurried in a small volume of water. The solids were filtered, washed, and air-dried to yield the
- 25 phosphate ester of 2-(p-methoxybenzyl)-3-methyl-4-hydroxy-5-propyl-7-chlorobenzofuran.

- 30 ¹NMR: 0.93 (t, 3H, J=7 Hz, CH₃), 1.60 (sextet, 2H, J=7 Hz, CH₂), 2.27 (s, 3H, CH₃), 2.87 (t, J=7 Hz, 2H, CH₂), 3.80 (s, 3H, CH₃), 4.00 (s, 2H, CH₂), 6.83 (d, 2H, J=9 Hz, protons ortho to

0165810

2882P/1043A

2884P/1045A

- 132 -

171411A

methoxy), 7.10 (d, 2H, J=9 Hz, protons meta to
methoxy), 7.15 (s, 1H, H₆).

Anal. Calcd. C, 56.54; H, 5.18; Cl, 8.35; P, 7.30.

5

Found: C, 56.59; H, 5.21; Cl, 8.52; P, 7.43.

10

15

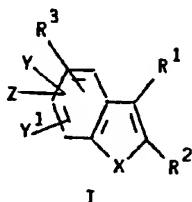
20

25

30

WHAT IS CLAIMED IS:

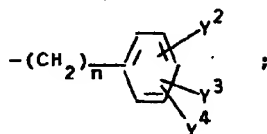
1. The compound of the formula:



wherein:

each R^1 is independently hydrogen or C_1 to C_6 alkyl;

15 R^2 is hydrogen, C_1 to C_6 alkyl, $-(CH_2)_n$ -Het-Y, or



25 R^3 is hydroxyl, $O-\overset{\overset{O}{\parallel}}{C}-R^1$, $O-\overset{\overset{O}{\parallel}}{C}-OR^4$, $OCOCH_2CH_2COOH$, OSO_3H , or OPO_3H_2 ;

each R^4 is independently C_1 to C_6 alkyl;

each R^5 is independently H, C_1 to C_6 alkyl, or both

30 R^5 s join to form a 5- or 6-membered ring with the N to which they are attached;

Het is a heterocyclic group selected from
pyridine, pyrazine, pyrimidine, oxazole,
pyrazole, oxadiazole, tetrazole, quinoline,
thiophene, furan, pyrrole, thiazole, thiadiazole,
or imidazole;

X is O, S, SO, SO₂;

Y, Y¹, Y², Y³, Y⁴ and Z are each
independently H, halogen, OH.

C₁ to C₆ alkyl, C₂ to C₆ alkenyl,

-COOR¹, -COR¹, nitro,

C₁ to C₆ alkoxy, C₁ to C₆ alkylthio,

-CH₂SR¹, OCH₂CO₂R¹,

-CON $\begin{matrix} \diagup R^1 \\ \diagdown R^1 \end{matrix}$, -SCF₃ ,

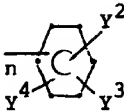
-SO₂N $\begin{matrix} \diagup R^1 \\ \diagdown R^1 \end{matrix}$ -CN, CF₃, or -NR⁵R⁵;

and each n is independently 0 to 10;

with the provisos that:

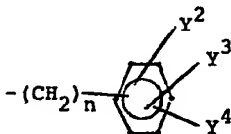
(a) not all of R¹, R², Y, Y¹, Y², Y³, Y⁴, and Z are
simultaneously H;

(b) when up to 2 of R¹, R², Y, Y¹, and Z are C₁ to C₂
alkyl, and the others of R¹, R², Y, Y¹, and Z are H,
then R³ is not OH; and

(c) when n in $-(CH_2)_n$  is 0 and one of R^3 , Y , Y^1

or Z is OH, then R^1 is not H or C_1 to C_2 alkyl;
and the pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 wherein:
each R^1 is C_1 to C_3 alkyl;
 R^2 is hydrogen, C_1 to C_3 alkyl,



or $-(CH_2)_n$ -Het- Y ;

R^3 is hydroxyl, $O-C(=O)-R^1$, $O-C(=O)-OR^4$, $OCOCH^2CH^2COOH$, OSO^3H ,
or OPO^3H_2 ;

each R^4 is independently C_1 to C_3 alkyl;

Het is heterocyclic group selected from pyridine,
quinoline, thiazole, thiadiazole, or imidazole;

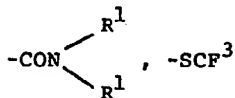
X is O or S;

Y , Y^1 , Y^2 , Y^3 , Y^4 and Z are each

independently H, halogen C_1 to C_3 alkyl, C_2

or C_3 alkenyl, $-COOR^1$, $-COR^1$, C_1 to C_3

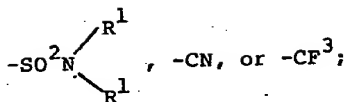
alkoxy, C_1 to C_3 alkylthio, $-CH_2SR^1$,



2950P/1045A

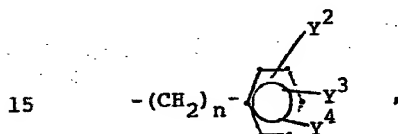
- 136 -

17141Y



- 5 Y^2 is also $\text{OCH}_2\text{CO}_2\text{R}^1$;
each n is independently 0 to 4;
and the pharmaceutically acceptable salts thereof.

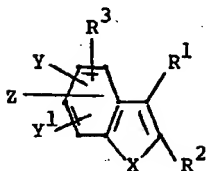
- 10 3. A compound according to Claim 2 wherein:
each R^1 is methyl;
 R^2 is hydrogen,



- or $-\text{CH}_2\text{-Het-Y}$;
 R^3 is 4-hydroxyl, 4- OSO_3H , or 4- OPO_3H_2 ;
20 Het is a pyridine;
 $n = 1$ or 2 ;
 X is O; and
 Y , Y^1 , Y^2 , Y^3 , Y^4 , and Z are each independently
H, fluorine, chlorine, methyl, propyl, allyl,
25 $-\text{COOR}^1$, $-\text{COR}^1$, methoxy, methylthio,
 $-\text{CH}_2\text{SR}^1$, or $-\text{CF}_3$;
and the pharmaceutically acceptable salts thereof.

30

4. The compounds of Claim 1:



wherein:

10

15

20

25

30

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
2	CH ₃	H	4-OOCCH ₃	O	H	H	-	-	-
4	CH ₃	H	4-OH	O	5-allyl	H	-	-	-
5	CH ₃	H	4-OH	O	5-propyl	H	-	-	-
6	CH ₃	H	4-OOCCH ₃	O	5-propyl	H	-	-	-
7	CH ₃	H	4-OH	O	7-propyl	H	-	-	-
8	CH ₃	C ₂ H ₅	4-OH	O	5-allyl	H	-	-	H
9	CH ₃	CH ₂ CH ₃	4-OH	O	5-propyl	H	H	H	-
10	C ₃ H ₇	H	4-OH	O	H	H	-	-	-
11	C ₃ H ₇	H	4-allyl	O	H	H	-	-	-
12	C ₃ H ₇	H	4-OH	O	5-allyl	H	-	-	-
13	C ₆ H ₅	H	4-OH	O	H	H	-	-	H
14	CH ₃	CH ₂ 4-pyridyl	4-OH	O	5-propyl	H	H	H	H
15	CH ₃	CH ₂ C ₆ H ₅	5-OH	O	6-OH	H	H	H	H
16	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OH	H	H
17	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	-
21	CH ₃	H	5,6-OCH ₂ O	O	H	H	-	-	-
22	CH ₃	H	4-OCH ₃	O	7-propyl	H	-	-	-
24	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₃	O	5-propyl	H	4-OH	H	H

	R^1	R^2	R^3	X	Y	Y^1	Y^2	Y^3	Y^4
25	CH_3	$CH_2C_6H_5$	$4-OOC_2CH_3$	0	5-propyl	H	$4-OCH_3$	H	H
26	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	H	H	H
27	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	4-OH	H	H
28	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	$4-OCH_3$	H	H
29	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	4-F	H	H
30	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	4-Cl	H	H
31	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	$4-N(CH_3)_2$	H	H
32	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	H	4-F	H	H
33	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	H	4-Cl	H	H
34	CH_3	$CH_2C_6H_5$	4-OH	0	5-propyl	H	$4-N(CH_3)_2$	H	H
35	C_3H_7	$CH_2C_6H_5$	4-OH	0	5-propyl	H	H	H	H
36	C_3H_7	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	4-F	H	H
37	C_3H_7	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	4-OH	H	H
38	C_3H_7	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	$4-OCH_3$	H	H
39	C_3H_7	$CH_2C_6H_5$	4-OH	0	5-propyl	7-F	$4-N(CH_3)_2$	H	H
40	C_3H_7	$CH_2C_6H_5$	4-OH	0	5-propyl	H	$4-OCH_3$	H	H

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
41	C ₃ H ₇	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OH	H	H
42	C ₃ H ₇	CH ₂ C ₆ H ₅	5-OH	O	6-OH	H	4-OCH ₃	H	H
43	C ₃ H ₇	CH ₂ C ₆ H ₅	5-OH	O	6-OH	H	4-F	H	H
44	CH ₃	CH ₂ C ₆ H ₅	5-OH	O	H	H	4-OCH ₃	H	H
45	CH ₃	CH ₂ C ₆ H ₅	6-OH	O	5-propyl	H	4-OCH ₃	H	H
46	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-allyl	H	4-OCH ₃	H	H
48	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OH ₂ SOCH ₃	H	4-OCH ₃	H	H
49	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OH ₂ OCH ₃	H	4-OCH ₃	H	H
50	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	H	H	H
51	CH ₃	CH ₂ 6-quinoline	4-OH	O	5-propyl	H	H	H	H
52	CH ₃	CH ₂ 3-furan	4-OH	O	5-propyl	H	H	H	H
53	CH ₃	CH ₂ 3-thiophene	4-OH	O	5-propyl	H	H	H	H
54	CH ₃	CH ₂ 3-pyrrole	4-OH	O	5-propyl	H	H	H	H
55	CH ₃	CH ₂ 2-pyridyl	4-OH	O	5-propyl	H	H	H	H
56	CH ₃	CH ₂ -thiadiazole	4-OH	O	5-propyl	H	H	H	H
57	CH ₃	CH ₂ thiazole	4-OH	O	5-propyl	H	H	H	H
		CH ₂ CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
58	CH ₃	C ₆ H ₅	4-OH	O	5-propyl	H	4-OCH ₃	H	H
59	CH ₃	C ₆ H ₅	4-OH	O	5-propyl	H	4-OH	H	H
60	CH ₃	C ₆ H ₅	4-OH	O	5-propyl	H	4-F	H	H
61	CH ₃	C ₆ H ₅	4-OH	S	5-propyl	H	4-OCH ₃	H	H
62	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	H	H	H	H
63	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	H	4-OCH ₃	H	H
64	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	7-F	4-OCH ₃	H	H
65	CH ₃	CH ₂ C ₆ H ₅	4-OH	S	5-propyl	7-F	4-F	H	H
66	CH ₃	CH ₂ C ₆ H ₅	5-OH	S	6-OH	H	4-OCH ₃	H	H
67	CH ₃	CH ₂ C ₆ H ₅	4-OH	SO	5-propyl	7-F	4-OCH ₃	H	H
68	CH ₃	CH ₂ C ₆ H ₅	4-OH	SO ₂	5-propyl	7-F	4-OCH ₃	H	H
69	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OCH ₃	7-F	4-OCH ₃	H	H
70	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-OCH ₃	7-F	4-OCH ₃	H	H
72	CH ₃	COCH ₂ C ₆ H ₅	4-OH	O	H	H	4-Cl	H	H
73	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OCH ₃	3-OH	H
74	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-Br	H	H
75	CH ₃	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	H	4-Cl	H	H

0165810

- 142 -

17141Y

	R^1	R^2	R^3	X	Y	Y^1	Y^2	Y^3	Y^4
76	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	7-Cl	4-F	H	H
77	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OAc	H	H
78	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	H	4-OH	H	H
79	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OH	H	H
80	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	H	H	4-OH	H	H
81	CH ₃	CH ₂ C ₆ H ₅	7-OH	0	H	H	4-OCH ₃	H	H
82	CH ₃	CH ₂ C ₆ H ₅	4-Oallyl	0	H	H	4-OCH ₃	H	H
84	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-Cl	4-OCH ₃	H	H
85	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	7-F	4-OCH ₃	H	H
86	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
87	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	0	5-propyl	7-F	4-OCH ₃	H	H
88	CH ₃	CH ₂ C ₆ H ₅	4-OOC ₂ CH ₃	0	5-propyl	7-Cl	4-OCH ₃	H	H
89	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Br	4-OCH ₃	H	H
90	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
91	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-allyl	H	4-OCH ₃	H	H
92	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
93	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	1-propyl	H	4-OCH ₃	H	H
94	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-OH ₃	4-OCH ₃	H	H
95	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-Pr	4-OCH ₃	H	H
96	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-Cl	1-Pr	4-OCH ₃	H	H
97	CH ₃	CH ₂ C ₆ H ₅	4-OPh ₃ H ₂	0	5-propyl	1-Cl	4-OCH ₃	H	H
98	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	5-propyl	1-F	4-OCH ₃	H	H
99	CH ₃	CH ₂ C ₆ H ₅	4-OOCCH ₂ CH ₂ CO ₂ H	0	5-propyl	1-Cl	4-OCH ₃	H	H
100	CH ₃	CH ₂ C ₆ H ₅	5-OAc	0	4-propyl	H	4-OCH ₃	H	H
101	CH ₃	CH ₂ C ₆ H ₅	5-OOC ₂ CH ₃	0	4-propyl	H	4-OCH ₃	H	H
102	CH ₃	CH ₂ C ₆ H ₅	5-OH	0	4-propyl	H	4-OCH ₃	H	H
103	CH ₃	CH ₂ C ₆ H ₅	4-OAc	0	5-propyl	1-Cl	4-OCH ₂ CO ₂ Et	H	H
105	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-Cl	4-OCH ₂ CO ₂ H	H	H
107	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	H	H	H
108	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-Cl	H	H	H
109	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-Cl	4-OH	H	H

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
110	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OHc	0	H	H	4-OCH ₃	H	H
111	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	H	H	4-OCH ₃	H	H
112	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
113	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OH	0	5-propyl	H	4-OCH ₃	H	H
114	CH ₃	CH ₂ CH ₂ C ₆ H ₅	4-OCH ₃ H	0	5-propyl	7-Cl	4-OCH ₃	H	H
115	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-Cl	4-OCH ₃	H	H
116	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
117	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	7-Cl	4-OCH ₃	H	H
118	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
119	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
120	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
121	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ H	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
122	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ CH ₂ CO ₂ H	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
123	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ H ₂	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
124	CH ₃	CH ₂ C ₆ H ₅	4-OCH ₃ H ₂	0	CH ₂ SO ₂ CH ₃	7-Cl	4-OCH ₃	H	H
125	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	7-F	4-OCH ₃	H	H

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
126	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SO ₂ CH ₃	1-F	4-OCH ₃	H	H
127	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ COCH ₃	1-F	4-OCH ₃	H	H
128	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
129	CH ₃	CH ₂ C ₆ H ₅	4-OOSOCH ₂ CO ₂ H	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
130	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H ₂	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
131	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H ₂	0	CH ₂ SO ₂ CH ₃	1-F	4-OCH ₃	H	H
132	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
133	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
134	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
135	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	CH ₂ COCH ₃	1-F	4-OCH ₃	H	H
136	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
137	CH ₃	CH ₂ C ₆ H ₅	4-OOSOCH ₂ CO ₂ H	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
138	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H ₂	0	CH ₂ SOCH ₃	1-F	4-OCH ₃	H	H
139	CH ₃	CH ₂ C ₆ H ₅	4-OSO ₂ H ₂	0	CH ₂ SO ₂ CH ₃	1-F	4-OCH ₃	H	H
140	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-CO ₂ H	4-OCH ₃	H	H
141	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	1-Cl	4-OCH ₃	H	H

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
142	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-F	4-O ₂ H	H ¹	H
143	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH(OH)CH ₂ OH	7-Cl	4-O ₂ H	H	H
144	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH(OH)CH ₂ OH	7-F	4-O ₂ H	H	H
145	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH(OH)CH ₃	7-Cl	4-O ₂ H	H	H
146	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH(OH)CH ₃	7-F	4-O ₂ H	H	H
147	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-propyl	7-SO ₃ H	4-O ₂ H	H	H
148	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-CH ₂ CH ₂ OH	7-Cl	4-O ₂ H	H	H
149	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-C(OH) ₃	7-Cl	4-O ₂ H	H	H
150	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	5-C(OH) ₃	7-Cl	4-O ₂ H	H	H
151	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-Cl	4-CH ₃	H	H
152	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-CH ₃	4-CH ₃	H	H
153	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-F	4-CH ₃	H	H
154	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	H	4-CH ₃	H	H
155	CH ₃	CH ₂ tetrazol	4-OH	0	5-propyl	7-Pr	4-CH ₃	H	H
156	CH ₃	CH ₂ tetrazol	5-OH	0	5-propyl	7-Pr	4-CH ₃	H	H
157	CH ₃	CH ₂ C ₆ H ₅	4-OH	0	H	H	H	H	H

0165810

- 147 -

17141 Y

	R ¹	R ²	R ³	X	Y	Y ¹	Y ²	Y ³	Y ⁴
158	CH ₃	CH ₂ C ₆ H ₅	4-OHc	O	H	H	H	H	H
159	CH(CH ₃) ₂	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OH ₃ O	H	H
160	CH(CH ₃) ₂	CH ₂ C ₆ H ₅	4-OH	O	5-propyl	7-Cl	4-OH ₃ O	H	H
161	CH(CH ₃) ₂	H	5-OH	O	H	H	-	-	-
162	CH(CH ₃) ₂	H	4-OH	O	H	H	-	-	-

5. A pharmaceutical composition useful in inhibiting leukotriene formation in mammals comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.
6. A composition according to Claim 5 additionally comprising an effective amount of a second active ingredient that is a non-steroidal anti-inflammatory drug; a peripheral analgesic agent; cyclooxygenase inhibitor; a leukotriene antagonist; a leukotriene inhibitor; an H_2 -receptor antagonist; an antihistaminic agent; a prostaglandin antagonist or a thromboxane antagonist.
7. A composition according to Claim 6, in which the weight ratio of the compound of Formula I to the second active ingredient ranges from 1000:1 to 1:1000.
8. A composition according to Claim 6 or 7, in which the second active ingredient is a non-steroidal anti-inflammatory drug.
9. A compound according to Claim 1 for use in inhibiting leukotriene action in mammals.
10. A compound according to Claim 1 for use in treating or ameliorating allergic conditions, asthma, psoriasis, pain, inflammation, or cardiovascular conditions in mammals or inducing cytoprotection in mammals.